The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder

Additional Resources: Evidence to Decision Tables, Summary of Evidence, Relevant Citations, CGC Judgements

Table of Contents

Behavioral Treatment

Table 1. Contingency Management

Recommendation: Contingency management (CM) should be a primary component of the treatment plan in conjunction with other psychosocial treatments for StUD.

Clinical Question Summary Table

Clinical Question	1. Is Contingency Management an effective and appropriate treatment for StUD? 2. Does the addition of another treatment to CM improve outcomes for StUD? 3. What contextual factors and implementation strategies may influence the effects of CM?
Population	Patients with stimulant use disorder
Intervention	Contingency Management delivered with or without an additional psychosocial treatment for StUD (Typically CBT)
Comparison	Contingency Management delivered and/or a psychosocial treatment used for StUD (Typically CBT)
Main Outcomes	Stimulant use, treatment retention, psychiatric symptoms, risky behavior
Setting	Inpatient or outpatient specialty SUD
Background & Definitions	Contingency Management (CM) is... **CBT**: Cognitive Behavioral Therapy, **CM**: Contingency Management, **CRA:** Community reinforcement approach, **GCBT**: Gay-specific Cognitive Behavioral Therapy **ARTEMIS:** Affect Regulation Treatment to Enhance Methamphetamine Intervention Success, **SBCM:** Strength based case management **MBI**: Meditation-based interventions
Abbreviations	**ASI:** Addiction Severity Index, **ATS**: Amphetamine-type stimulants, **ATStUD**: Amphetamine-type stimulant use disorder, **BDI:** Beck Depression Inventory, **CBT**: Cognitive Behavioral Therapy, **CM**: Contingency Management, **CoUD:** Cocaine use disorder, **CRA:** Community reinforcement approach, **GAD**: Generalized anxiety disorder, **GCBT**: Gay-specific Cognitive Behavioral Therapy, **MA**: Methamphetamine, **MaUD**: Methamphetamine Use Disorder, **MBI**: Meditation-based interventions, **MDD**: Major Depressive Disorder, **MMT**: Methadone maintenance therapy, **MSM:** Men who have sex with men, **N:** Number, **NCR**= Non-conditional rewards (CM placebo), **n.r.**= Not Reported, **NSD**: No significant difference, **OPT**: Outpatient treatment, **RoB:** Risk of Bias, **RP:** Relapse prevention, **SMD**: Standardized Mean Difference, **SMI**: Severe mental illness **StUD:** Stimulant use disorder, **TAU**: Treatment as Usual, **UDS:** Urine drug screen
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

CM vs Non-Contingent Rewards (NCR)

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 21 RCTs • **CM > NCR** @ 12 weeks: SMD 0.52, 95% CI 0.22–0.81, p=n.r. Pairwise meta-analysis • **CM > NCR** @ 12 weeks: 5 RCTs, n=588, SMD 0.61, 95% CI 0.17–1.05, p=n.r. ; I-squared=83.1%, p=0.000: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM + TAU vs NCR + TAU vs CM + CBT + TAU vs NCR + CBT + TAU) **High RoB;** Petry 2012b (n=442 CoUD, CM + TAU vs TAU) **Unclear RoB;** Silverman 1996 (n=37 CoUD/abuse & OUD in MMT, 3 mo CM+CRA vs NCR+CRA) **Unclear RoB;** Silverman 1998 (n=59 Cocaine abuse & OUD in MMT, 3 mo CM+CT vs non-CM+CT) **Unclear RoB;** Umbricht 2014 (n=171 CoUD & MMT, CM + Topiramate/Placebo vs NCR + Topiramate/Placebo) **Low RoB**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
Continuous stimulant abstinence@ trial end	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 25 RCTs • **CM > NCR** @ trial end: SMD 0.46, 95% CI 0.22–0.7, p=n.r. Pairwise meta-analysis • **CM > NCR** @ trial end: 6 RCTs, n=675, SMD 0.55, 95% CI 0.19–0.9, p=n.r. ; I-squared=79%, p=0.000: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM + TAU vs NCR + TAU vs CM + CBT + TAU vs NCR + CBT + TAU) High RoB; Petry 2012b (n=442 CoUD, CM + TAU vs TAU) Unclear RoB; Poling 2006 (n=106 Cocaine abuse & OUD in MMT, CM + CBT + Bupropion/Placebo vs NCR + CBT + Bupropion/Placebo) Unclear RoB; Silverman 1996 (n=37 CoUD/abuse & OUD in MMT, 3 mo CM+CRA vs NCR+CRA) Unclear RoB; Silverman 1998 (n=59 Cocaine abuse & OUD in MMT, 3 mo CM+CT vs non-CM+CT) Unclear RoB; Umbricht 2014 (n=171 CoUD & MMT, CM + Topiramate/Placebo vs NCR + Topiramate/Placebo) Low RoB	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)

		Meta-analysis: Minozzi 2016[2] (Supplemental)	**CM > NCR** in use of cocaine for at least 5 consecutive weeks @ end of treatment (2 RCTs, n=96, RR 8.11, 95% CI 1.62–40.55, p=0.01) • Silverman 1996 (n=37 CoUD/abuse & OUD in MMT, 3 mo CM+CRA vs NCR+CRA); Silverman 1998 (n=59 Cocaine abuse & OUD in MMT, 3 mo CM+CT vs non-CM+CT)	Cochrane Review
Stimulant abstinence rate @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 42 RCTs • **CM > NCR** at 12 weeks: OR 2.56, 95% CI 1.68–3.91, p=n.r. Pairwise meta-analysis • **CM > NCR** at 12 weeks: 9 RCTs, n=1156, OR 2.65, 95% CI 1.58–4.43, p=n.r.; I-squared=67.9%, p=0.002 o Epstein 2003 High RoB; Ghitza 2007b Unclear RoB; Landovitz 2015 High RoB; McDonell 2013 Unclear RoB; Petry 2012b Unclear RoB; Poling 2006 Unclear RoB; Silverman 1996 Unclear RoB; Silverman 1998 Unclear RoB; Umbricht 2014 Low RoB	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence rate @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 46 RCTs • **CM > NCR** at trial end: OR 2.59, 95% CI 1.7–3.93, p=<0.001. Confidence in estimate: Moderate Pairwise meta-analysis • **CM > NCR** at trial end: 9 RCTs, n=1137, OR 2.69, 95% CI 1.61–4.51, p=n.r.; I-squared=67.8%, p=0.002 o Epstein 2003 High RoB; Ghitza 2007b Unclear RoB; Landovitz 2015 High RoB; McDonell 2013 Unclear RoB; Petry 2012b Unclear RoB; Poling 2006 Unclear RoB; Silverman 1996 Unclear RoB; Silverman 1998 Unclear RoB; Umbricht 2014 Low RoB Author evaluation of the quality of mixed direct and indirect evidence • Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Cocaine/MA abstinence rate (% UDS-)
		Meta-analysis: Sayegh 2017[3] (Moderate)	Included studies of CM with or without background treatment vs NCR and/or background treatment targeting stimulant use reduction (RCTs=14). Included amphetamine, cocaine, methamphetamine use disorder and co-occurring SUD populations. **CM (+/- other) > TAU (+/- other)**: CM was effective at reducing stimulant use (UDS+) even after the end of treatment (0-3 months), but this effect dissipated over time. • 0-3 months: n=11, Cohen's d=0.62, 95% CI 0.01–1.24, p<0.05	ATS/Cocaine/MA use disorder

			○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU); Higgins 1994 (n=40 CoUD, CRA+CM vs CRA); McDonell 2013 (n=176 CoUD/MaUD & SMI [schizophrenia, bipolar, MDD], CM+TAU vs NCR+TAU); McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Petry 2005c Effect (n=415 CoUD/MaUD); Petry 2007 (n=74 CoUD & OUD); Petry 2015 (n=240); Poling 2006 (n=106 Cocaine abuse & OUD); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT); Rowan-Szal 2005 (n=61 cocaine use & OUD); Silverman 1998 (n=59 Cocaine abuse & OUD • 3-6 months: n=7, d=0.01, 95% CI -0.18 to 0.19, p=0.95 ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU), Higgins 1994 (n=40 CoUD, CRA+CM vs CRA), McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU), Petry 2007 (n=74 CoUD & OUD), Petry 2012b, Shoptaw 2005 (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT)	
Stimulant abstinence rate @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 32 RCTs • **CM > NCR** at furthest follow-up: OR 1.86, 95% CI 1.31–2.66, p=n.r. Pairwise meta-analysis • **CM > NCR** at furthest follow-up: 7 RCTs, n=879, OR 2.08, 95% CI 1.22–3.54, p=n.r.; I-squared=62.4%, p=0.014 ○ Epstein 2003 High RoB, Ghitza 2007b Unclear RoB, Landovitz 2015 High RoB, McDonell 2013 Unclear RoB, Petry 2012b Unclear RoB, Silverman 1996 Unclear RoB, Silverman 1998 Unclear RoB,	Cocaine/MA abstinence rate (% UDS-)
		Meta-analysis: Minozzi 2016[2] (Supplemental)	**No CM > CM** @ furthest follow-up (1 RCT, n=126, RR 0.54, 95% CI 0.42–0.7, p<0.001) • McDonell 2013 (n=176 CoUD/MaUD & SMI [schizophrenia, bipolar, MDD], CM+TAU vs NCR+TAU) UDS- 46% vs 86%	Cochrane Review
Treatment retention @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 41 RCTs • **No difference** at 12 weeks Pairwise meta-analysis • **No difference** at 12 weeks: 8 RCTs, n=931; I-squared=42.5%, p=0.095: ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB, Ghitza 2007b Unclear RoB,	Dropout rate (%n)

			Landovitz 2015 Unclear RoB, McDonell 2013 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) Unclear RoB, Poling 2006 Unclear RoB, Silverman 1996 Unclear RoB, Silverman 1998 Unclear RoB, Umbricht 2014 Low RoB	
Treatment retention @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 43 RCTs • **No difference** at trial end. Confidence in estimate: Very low Pairwise meta-analysis • **No difference** at trial end: 8 RCTs, n=931; I-squared=36.9%, p=0.134: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Ghitza 2007b Unclear RoB, Landovitz 2015 Unclear RoB, McDonell 2013 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) Unclear RoB, Poling 2006 Unclear RoB, Silverman 1996 Unclear RoB, Silverman 1998 Unclear RoB, Umbricht 2014 Low RoB Author evaluation of the quality of mixed direct and indirect evidence • Confidence in trial end estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)
		Meta-analysis: Minozzi 2016[2] (Supplemental)	**No significant difference** in dropout rate (%n) (4 RCTs, n=464, RR 1.00, 95% CI 0.59–1.70, p=1) • McDonnell 2013 (n=176 CoUD/MaUD & SMI [schizophrenia, bipolar, MDD], CM+TAU vs NCR+TAU); Poling 2006 (n=106 Cocaine abuse & OUD in MMT, CM+CBT+Bupropion/Placebo vs NCR+CBT+Bupropion/Placebo); Schottenfeld 2011 (n=145 CoUD women, 6 mo CM+CRA vs NCR+CRA vs CM+TSF vs NCR+TSF); Silverman 1996 (n=37 CoUD/abuse & OUD in MMT, 3 mo CM+CRA vs NCR+CRA)	Cochrane Review

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CM vs TAU

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments

Outcome Importance: Critical				
Continuous stimulant abstinence@ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 21 RCTs • **CM > TAU** @ 12 weeks: SMD 0.62, 95% CI 0.43–0.8, p=n.r. Pairwise meta-analysis • **CM > TAU** @12 weeks MA: 11 RCTs, n=1792, SMD 0.56, 95% CI 0.41–0.71, p=n.r.; I-squared=48.4%, p=0.036: o Festinger 2014 Unclear RoB; Kirby 1998 Unclear RoB; Miguel 2016 Unclear RoB; Peirce 2006 High RoB; Petry 2002 Unclear RoB; Petry 2005b Unclear RoB Prize; Petry 2005c Effect Unclear RoB; Petry 2012a Unclear RoB; Petry 2012b Unclear RoB; Petry 2013 Unclear RoB; Roll 2013 High RoB	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
Continuous stimulant abstinence@ trial end	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 25 RCTs • **CM > TAU** @ trial end: SMD 0.6, 95% CI 0.43–0.76, p=n.r. Pairwise meta-analysis • **CM > TAU** @ trial end: 11 RCTs, n=1792, SMD 0.56, 95% CI 0.41–0.71, p=n.r.; I-squared=48.4%, p=0.036: o Festinger 2014 Unclear RoB, Kirby 1998 Unclear RoB, Miguel 2016 Unclear RoB, Peirce 2006 High RoB, Petry 2002 Unclear RoB, Petry 2005b Unclear RoB Prize, Petry 2005c Effect Unclear RoB, Petry 2012a Unclear RoB, Petry 2012b Unclear RoB, Petry 2013 Unclear RoB, Roll 2013 High RoB	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
Stimulant abstinence rate @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 42 RCTs • **CM > TAU** @ 12 weeks: OR 2.29, 95% CI 1.62-3.24, p=n.r. Pairwise meta-analysis • **CM > TAU** @ 12 weeks: 14 RCTs, n=1984, OR 0.65, 95% CI 0.49–0.87, p=n.r.; I-squared=57.1%, p=0.004: o Hagedorn 2013 High RoB, Kirby 1998 study 1 & study 2 Unclear RoB, Ledgerwood 2006 High RoB, Menza 2010 Low RoB, Miguel 2016 Unclear RoB, Peirce 2006 High RoB, Petry 2002 Unclear RoB, Petry 2005b Prize Unclear RoB, Petry 2005c Effect Unclear RoB, Petry 2007 Unclear RoB, Petry 2012a Unclear RoB, Petry 2013 Unclear RoB, Rawson 2002 Unclear RoB, Roll 2013 High RoB	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence rate@ trial	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 46 RCTs • **CM > TAU** @ trial end: OR 2.22, 95% CI 1.59–3.1, p<0.001. Confidence in estimate: Moderate	Cocaine/MA abstinence rate (% UDS-)

end@ trial end			Pairwise meta-analysis • **CM > TAU** @ trial end: 14 RCTs, n=1984, OR 0.65, 95% CI 0.49–0.87, p=n.r. ; I-squared=57.1%, p=0.004: o Hagedorn 2013 High RoB; Kirby 1998 study 1 & study 2 Unclear RoB; Ledgerwood 2006 High RoB; Menza 2010 Low RoB; Miguel 2016 Unclear RoB; Peirce 2006 High RoB; Petry 2002 Unclear RoB; Petry 2005b Prize Unclear RoB; Petry 2005c Effect Unclear RoB; Petry 2007 Unclear RoB; Petry 2012a Unclear RoB; Petry 2013 Unclear RoB; Rawson 2002 Unclear RoB; Roll 2013 High RoB Author evaluation of the quality of mixed direct and indirect evidence • Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Meta-analysis: Sayegh 2017[3] (Moderate)	Included studies of CM with or without background treatment vs NCR and/or background treatment targeting stimulant use reduction (RCTs=14). Included amphetamine, cocaine, methamphetamine use disorder and co-occurring SUD populations. **CM** was effective at reducing stimulant use (UDS+) even after the end of treatment (0-3 months): n=11, Cohens d=0.62, 95% CI 0.01–1.24, p<0.05 o Epstein 2003 (n=286 CoUD & OUD in MMT); Higgins 1994 (n=40 CoUD; McDonell 2013 (n=176 CoUD/MaUD & SMI); McKay 2010 (n=100 CoUD); Petry 2015 (n=240); Poling 2006 (n=106 Cocaine abuse & OUD); Rowan-Szal 2005 (n=61 cocaine use & OUD); Silverman 1998 (n=59 Cocaine abuse & OUD	
Stimulant abstinence rate @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 32 RCTs • **?** Pairwise meta-analysis • **No difference** @ furthest follow-up: 9 RCTs, n=1265; I-squared=25.2%, p=0.219: o Hagedorn 2013 High RoB; Menza 2010 Low RoB; Peirce 2006 High RoB,; Petry 2002 Unclear RoB; Petry 2005c Effect Unclear RoB; Petry 2007 Unclear RoB; Petry 2012a Unclear RoB; Petry 2012b Unclear RoB; Rawson 2002 Unclear RoB	Cocaine/MA abstinence rate (% UDS-)
		Meta-analysis: Sayegh 2017[3] (Moderate)	Included studies of CM with or without background treatment vs NCR and/or background treatment targeting stimulant use reduction (RCTs=14). Included amphetamine, cocaine, methamphetamine use disorder and co-occurring SUD populations. **CM** effect at reducing stimulant use (UDS+) dissipated over time (3-6 months): n=7, d=0.01, 95% CI -0.18 to 0.19, p=0.95	

			• Epstein 2003 (n=286 CoUD & OUD in MMT); Higgins 1994 (n=40 CoUD); McKay 2010 (n=100 CoUD); Shoptaw 2005a (n=162 MaUD MSM)	

		Meta-analysis: Ginley 2021[4] (Supplemental)	**CM** participants more likely to be stimulant abstinent (UDS-) up to a year following CM discontinuation than participants who received a nonspecific therapy, a nonspecific comprehensive therapy, or a specific therapy comparison condition (RCTs=15, OR 1.219, 95% CI 1.032–1.441, p=.02). Longer length of active treatment was found to significantly improve long-term abstinence.
			• Medication-assisted treatment clinics:
			  ○ Petry 2015 (n=240); Silverman 2004 (n=78)
			• Other settings:
			  ○ Alessi 2007 (n=103); Chudzynski 2015 (n=119); McDonell 2013 (n=176 CoUD/MaUD & SMI); Petry 2005a Vouchers (n=142); Rawson 2006 (n=177); Roll 2013 (n=118 MaUD)
				Population is mixed across SUDs. All stimulant studies are covered in other meta-analyses.

Treatment retention @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 41 RCTs • **CM > TAU** @12 weeks: OR 1.39, 95% CI 1.09–1.78, p=n.r. Pairwise meta-analysis • **CM > TAU** @ 12 weeks: 12 RCTs, n=1686, OR 0.65, 95% CI 0.49–0.87, p=n.r. ; I-squared=26.3%, p=0.186: ○ Hagedorn 2013 High RoB; Kirby 1998 study 1 Unclear RoB; Kirby 1998 study 2 Unclear RoB; Menza 2010 Low RoB; Miguel 2016 Unclear RoB; Peirce 2006 High RoB; Petry 2002 Unclear RoB; Petry 2005b Prize Unclear RoB; Petry 2005c Effect Unclear RoB; Petry 2007 Unclear RoB; Petry 2012a Unclear RoB; Petry 2013 Unclear RoB; Roll 2013 High RoB	Dropout rate (%n)
Treatment retention @ trial end	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 43 RCTs • **CM > TAU** @ trial end: OR 1.41, 95% CI 1.1–1.82, p=0.007 Pairwise meta-analysis • **CM > TAU** @ trial end: 12 RCTs, n=1686, OR 0.65, 95% CI 0.49–0.87, p=n.r.; I-squared=26.3%, p=0.186 ○ Hagedorn 2013 High RoB; Kirby 1998 study 1 Unclear RoB; Kirby 1998 study 2 Unclear RoB; Menza 2010 Low RoB; Miguel 2016 Unclear RoB; Peirce 2006 High RoB; Petry 2002 Unclear RoB; Petry 2005b Prize Unclear RoB; Petry 2005c Effect Unclear RoB; Petry 2007 Unclear RoB; Petry 2012a Unclear RoB; Petry 2013 Unclear RoB; Roll 2013 High RoB Author evaluation of the quality of mixed direct and indirect evidence	Dropout rate (%n)

			• Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Outcome Importance: Important				
Sexual risk-taking behavior	Low	RCT: Menza 2010[5] (Supplemental)	**No difference** between CM alone and Referral alone during the intervention in percent self-reporting unprotected anal intercourse (UAI) with a partner of unknown or discordant HIV status (non-concordant UAI) (adjusted RR 0.80, 95% CI 0.47–1.35). • n=127 MA use non-tx seeking MSM, CM alone vs Referral resources	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CM vs CBT

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ 12 wks	High	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CM** compared to CBT: SMD (95% CI) = -0.56 (-0.88, -0.23), p=n.r. Network meta-analysis of 21 RCTS	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
			Positive for CM compared to CBT: 2 RCTs, 217 participants, SMD (95% CI) = -0.65 (-0.96, -0.034), p=n.r. I-squared=19.8%, p=0.264. Pairwise meta-analysis: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) Unclear RoB. CM alone > CBT Matrix Model alone**:** 5.1 vs 2.1 weeks	
Continuous stimulant	High		**Positive for CM** compared to CBT: SMD (95% CI) = -0.5 (-0.78, -0.23), p=n.r. Network meta-analysis of 25 RCTS	Longest duration (in weeks) of

abstinence @ trial end		Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CM** compared to CBT: SMD (95% CI) = -0.65 (-0.96, -0.34), p=n.r. Pairwise meta-analysis of 2 RCTs, 217 participants; I-squared=19.8%, p=0.264: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) Unclear RoB	cocaine/MA abstinence (UDS)
		RCT: Rawson 2006[6] (Supplemental)	**Positive for CM alone** compared to Matrix Model alone: igher percentage of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial compared to CBT Matrix Model alone (60% vs 34.5%). (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model)	
Stimulant abstinence @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis • **Positive for CM** compared to CBT: OR (95% CI) = 0.51 (0.33, 0.79), p=n.r. Pairwise meta-analysis • **Positive for CM** compared to CBT: OR (95% CI) = 0.43 (0.27, 0.68), p=n.r. 4 RCTs, 395 participants; I-squared=0%: ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB No sig diff bn groups; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) Unclear RoB **No sig diff bn groups;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) Unclear RoB **CM > CBT** 5.1 vs 2.1 weeks	
Stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis • **Positive for CM** compared to CBT: OR (95% CI) = 0.53 (0.35, 0.81), p=0.003. Pairwise meta-analysis • **Positive for CM** compared to CBT: OR (95% CI) = 0.43 (0.27, 0.68), p=n.r. 4 RCTs, 395 participants; I-squared=0%: ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) Unclear	

			RoB; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) Unclear RoB Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Low; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Meta-analysis: Minozzi 2016[2] (Supplemental)	**No difference** in abstinence rate (%n) @ end of treatment (1 RCT, n=55, RR 0.66 [0.38,1.16], p=0.15)	Cochrane Review
		Systematic review: AshaRani 2020[7] (Moderate-High)	**CM** showed the strongest evidence in promoting abstinence and reducing methamphetamine use, although CBT was also effective. "CM, CBT and exercise demonstrated clear efficacy in reducing METH use and thus should continue to be the first line of treatment for METH dependence in the absence of effective pharmacotherapy" (p. 17).	
		Systematic review: Farronato 2013[8] (Supplemental)	**Positive for CM** compared to CBT: CM resulted in reduced cocaine use during active treatment in all eight included RCTs (n=1093). CBT demonstrated less reliable benefit with no positive effect during active treatment, but showed delayed positive results in three out of five trials. • Kirby 1998 (n=90 CoUD; McKay 2010 (n=100 CoUD); Rowan-Szal 2005 (n=61 cocaine use & OU); Schmitz 2008 (n=161 CoUD); Schmitz 2009 (n=87 CoUD & AUD)	
Stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis • **No difference** Pairwise meta-analysis • **No difference**. 4 RCTs, 395 participants; I-squared=0%: ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) Unclear RoB; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) Unclear RoB	
		Meta-analysis: Minozzi 2016[2] (Supplemental)	**No difference** in abstinence rate (%n) (1 RCT, n=55, RR 1.17 [0.73, 1.87], p=0.51)	Cochrane Review

		Systematic review: Farronato 2013[8] (Supplemental)	**CBT = CM**: "In 3 of the 5 studies with follow-up appointments, a positive effect of **CBT** emerged post-treatment... so-called sleeper effects." 5 RCTs, n=732: • McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Rowan-Szal 2005 (n=61 cocaine use & OUD in MMT)	
Treatment retention @ 12 weeks	High	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** Network meta-analysis	Dropout rate (%n)
			No difference. Pairwise meta-analysis 2 RCTs, 213 participants; I-squared=0%: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) Unclear RoB **CM > CBT** 63% vs 40%	
Treatment retention @ trial end	High	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis • **No difference**: OR (95% CI) = 1.04 (0.73, 1.48), p=0.838. Confidence in estimate: Moderate Pairwise meta-analysis • **No difference**. 2 RCTs, 213 participants; I-squared=0%. ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) High RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) Unclear RoB Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)
Duration of treatment	Moderate	RCT: Rawson 2006[6] (Supplemental)	**Positive for CM alone** compared to CBT Matrix Model alone: CM alone had more average weeks retained in treatment compared to CBT Matrix Model alone (12.6 vs 9 weeks) (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model vs CM+CBT Matrix Model)	
		RCT: Shoptaw 2005[9] (Supplemental)	**Positive for CM alone** compared to CBT Matrix Model alone: CM alone had more average weeks retained in treatment compared to CBT Matrix Model alone (12 vs 8.9 weeks) (n=162 OPT-seeking MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT)	
Outcome Importance: Important				

Stimulant craving	Moderate	Systematic review: AshaRani 2020[7] (Moderate-High)	**CM** showed the strongest evidence in reducing methamphetamine craving, although **CBT** was also effective.	
Sexual risk-taking behavior	Low	RCT: Shoptaw 2005[9] (Supplemental)	• **Positive for G-CBT** compared to CM alone, CBT Matrix Model alone, CM+CBT: G-CBT (tailored gay and bisexual men-specific Matrix Model CBT) showed greater initial reductions in unprotected receptive anal intercourse in the first 4 weeks of treatment relative to other conditions ($\chi 2$ (3) = 6.75, p < .01). This difference did not persist at 6- or 12-month follow-up. • **No difference** between CM alone, Matrix Model CBT alone, and CM+CBT; equivalent declines in self-reported sexual risk-taking behaviors such as incidence of unprotected anal intercourse and number of prior 30-day sexual partners • n=162 tx-seeking MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT	

CM vs CRA

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CM:** CM had a longer longest duration (in weeks) of cocaine/MA abstinence (UDS-) compared to CRA in a network meta-analysis of 50 RCTs: SMD (95% CI) = 0.82 (0.06, 1.59), p=n.r. No studies found for pairwise analysis.	
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**No effect:** Cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 50 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**No effect:** Cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 50 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CRA:** CRA > CM on cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 50 RCTs: OR (95% CI) = 0.41 (0.17, 0.97), p=n.r.	

			No studies found for pairwise analysis.	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**No effect:** Dropout rate (%n) in a network meta-analysis of 50 RCTs No studies found for pairwise analysis.	
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	**No effect:** Dropout rate (%n) in a network meta-analysis of 50 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

CM vs Other

Outcome	Strength of Evidencei	Evidence (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	<u>CM vs Twelve Step Facilitation</u> • **No difference** in longest duration (in weeks) of cocaine/meth abstinence at 12 weeks or end of trial found in the network meta-analysis of 50 RCTs.	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)

Stimulant abstinence rate	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	<u>CM vs Meditation-based treatments</u>
			• **No difference** at 12 weeks, trial end, or at the furthest follow-up found in network meta-analysis of 50 RCTs.
			• Confidence in end of trial estimate: Low
			
			<u>CM vs Supportive expressive psychodynamic therapy (SEPT)</u>
			• Network meta-analysis of 50 RCTs
			  ○ **CM > SEPT** at 12 weeks in network MA: OR (95% CI) = 3.64 (1.35, 9.82), p=n.r.
			  ○ **No difference** at trial end or furthest follow-up. Confidence in end of trial estimate: Low
			
			<u>CM vs Twelve Step Facilitation</u>
			• **No difference** in cocaine/meth abstinence rate (% UDS-) at 12 weeks, trial end, or at the furthest follow-up found in network meta-analysis of 50 RCTs.
			• Confidence in end of trial estimate: Low
				Cocaine/MA abstinence rate (% UDS-)

		Meta-analysis: Sayegh 2017[3] (Moderate)	**Significant effect of CM** on UDS-confirmed stimulant abstinence 0-3 months after the intervention across 11 studies (d [95% CI] = 0.62 [0.01, 1.24], p<0.05). All treatment-seeking populations. • Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) (d=0.27 [0.24, 0.77]); Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) (d=0.60 [0.13, 1.33]); McDonell 2013 (d=0.25 [0.09, 0.58]); McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU) (d=0.39 [0.22, 1.01]); Petry 2005b (d=0.48 [0.17, 1.12]); Petry 2007 (n=74 CoUD & OUD, d= 0.57 [0.09, 1.24]); Petry 2015 (n=240); Poling 2006 (n=106 Cocaine abuse & OUD); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT); Rowan-Szal 2005 (n=61 cocaine use & OUD in MMT); Silverman 1998 (n=59 Cocaine abuse & OUD in MMT, 3 mo CM+CT vs non-CM+CT) **No effect** 3-6 months after the intervention across 7 studies (d=.01 [-0.18, 0.19] p=0.95) • Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU); Higgins 1994 (n=40 CoUD, CRA+CM vs CRA); McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Petry 2007 (n=74 CoUD & OUD); Petry 2012b trial 1; Petry 2012b trial 2; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT)	
		Meta-analysis: Bentzley 2021[10] (Low)	Cocaine abstinence (reduced UDS+) "Only **contingency management** programs were significantly associated with an increased likelihood of having a negative test result for the presence of cocaine (OR, 2.13; 95%CI, 1.62-2.80), and this association remained significant in all sensitivity analyses." Higher odds ratio means greater reduction in cocaine use (greater likelihood of negative UDS) at end-of-trial. • Dallery 2001, Donlin 2008, Dunn 2014, Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU), Epstein 2009, Ghitza 2007b), Higgins 2003, Holtyn 2014, Jones 2004, Katz 2002, Kirby 2013, Kosten 2003, Liu 2014, Miguel 2016, Milby 2000, Milby 2008, Mooney 2009, Oliveto 2005, Petitjean 2014, Petry 2012b, Petry 2002, Petry 2004, Petry 2007 (n=74 CoUD & OUD), Poling 2006 (n=106 Cocaine abuse & OUD), Preston 2008, Preston 2001, Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT), Rowan-Szal 2005 (n=61 cocaine use & OUD), Schmitz 2008, Schottenfeld 2005, Sigmon 2004, Silverman 2004 (n=78), Silverman 2007, Silverman 1998 (n=59 Cocaine abuse & OUD, Silverman 1996, Silverman 1999, Wardle 2017, Petry 2005b Prize	

		Meta-analysis: Ginley 2021[4] (Supplemental)	**CM** participants more likely to be stimulant abstinent (UDS-) up to a year following CM discontinuation than participants who received a nonspecific therapy, a nonspecific comprehensive therapy, or a specific therapy comparison condition (RCTs=15, OR (95% CI) = 1.219 (1.032, 1.441), p=.02). Longer length of active treatment was found to significantly improve long-term abstinence.
			• Medication-assisted treatment clinics:
			  ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU), Petry 2012a, Petry 2015 (n=240), Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT), Silverman 2004 (n=78)
			• Other settings:
			  ○ Alessi 2007 (n=103), Chudzynski 2015, Hagedorn 2013, McDonell 2013, Petry 2005a Vouchers, Petry 2012b, Rawson 2006, Roll 2013, Shoptaw 2005a (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT)
				Population is mixed across SUDs. All stimulant studies are covered in other meta-analyses.

Treatment retention	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	<u>CM vs Meditation-based treatments</u>
			• **No difference** in dropout rate (%n) at 12 weeks or end of trial found in the network meta-analysis.
			• Confidence in end of trial estimate: Low
			
			<u>CM vs Supportive expressive psychodynamic therapy</u>
			• **No difference** in dropout rate (%n) at 12 weeks or end of trial found in the network meta-analysis.
			• Confidence in end of trial estimate: Moderate
			
			<u>CM vs Twelve Step Facilitation</u>
			• Network meta-analysis of 50 RCTs
			  ○ **CM > TSF** at 12 weeks: OR (95% CI) = 1.83 (1.19, 2.82), p=n.r.
			  ○ **CM > TSF** at trial end: OR (95% CI) = 1.75 (1.11, 2.75), p=0.015.
			  ○ Confidence in estimate: Moderate
				Dropout rate (%n)

CM+CBT vs CM

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])		Effect/Impact	Comments
Outcome Importance: Critical					

Continuous stimulant abstinence	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)		Network meta-analysis of 50 RCTs • **No difference** @ 12 weeks • **No difference** @ trial end Pairwise meta-analysis • **No difference** @ 12 weeks: 2 RCTs, 178 participants; I-squared=83.4%, p=0.014 o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Shoptaw 2005a (n=162 MaUD MSM, CM alone vs Matrix Model CBT alone vs CM+Matrix Model CBT vs GCBT) Unclear RoB **No diff bn groups** • **No difference** @ trial end: 3 RCTs, 384 participants; I-squared=72.9%, p=0.025 o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone) Unclear RoB; Shoptaw 2005a (n=162 MaUD MSM, CM alone vs Matrix Model CBT alone vs CM+Matrix Model CBT vs GCBT) Unclear RoB **No diff bn groups**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
		RCT: Rawson 2006[6] (Supplemental)		**No difference** between CM alone and CM+CBT in percentage of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial (overall rate=69.5%). (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model)	
Stimulant abstinence rate	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)		Network meta-analysis of 50 RCTs • **No difference** @ 12 weeks • **No difference** @ trial end. • **No difference** @ furthest follow-up Pairwise meta-analysis • **No difference** @ 12 weeks: 5 RCTs, 563 participants; I-squared=0%: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone) Unclear RoB; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs	Cocaine/MA abstinence rate (% UDS-)

				CM+CBT Matrix Model) Unclear RoB **No diff bn groups;** Shoptaw 2005a (n=162 MaUD MSM, CM alone vs Matrix Model CBT alone vs CM+Matrix Model CBT vs GCBT) Unclear RoB **No diff bn groups** • **No difference** @ trial end: 5 RCTs, 561 participants; I-squared=0%: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone) Unclear RoB; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model) Unclear RoB **No diff bn groups;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT) Unclear RoB **No diff bn groups** • **No difference** @ furthest follow-up: 5 RCTs, 563 participants; I-squared=2.5%, p=0.392: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model) Unclear RoB **No diff bn groups;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT) Unclear RoB **No diff bn groups** Author evaluation of the quality of mixed direct and indirect evidence @ trial end • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Systematic review: De Giorgi 2018[11] (Moderate)		"Combining RP with CM improved outcomes in cocaine users who had achieved initial abstinence (McKay, 2010)" (De Giorgi, 2018, p. 15). • McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU)	Glasner-Edwards 2017[12] p.03 (stim use) 2017;CM+MbI (31) vs CM (32) OR 0.78, p.03, those with GAD, 0.68.

		Systematic review: Farronato 2013[8] (Supplemental)		"Although additive effects related to cocaine abstinence of the combination of CM plus CBT through the follow-up period are shown in the trial by McKay et al (2010) and Epstein et al (2003), no additive effects were found in either trial by Rawson et al (2002, 2006) or in the trial by Rowan-Szal et al (2005). In the 2 studies by Rawson et al (2002, 2006), the CBT only and the CM only groups showed better drug-related outcomes compared with the combination group. In the trial by McKay et al (2010), the combination of CM plus relapse prevention showed the best drug-related outcomes and a trend in that direction was seen by Epstein et al (2003). The instruction that patients in the combination group had to attend relapse prevention session to be eligible for CM vouchers may have contributed to that effect in the study by McKay et al (2010)" (p. 13). • Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU); McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+TAU vs CM+TAU vs CBT+TAU vs TAU, TAU=MMT); Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model) No diff bn groups; Rowan-Szal 2005 (n=61 cocaine use & OUD in MMT)	
Duration of treatment	Low	RCT: Rawson 2006[6] (Supplemental)		**No difference** between CM alone and CM+CBT in average weeks retained in treatment (overall mean=12 weeks) (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model)	
		RCT: Shoptaw 2005[9] (Supplemental)		**No difference** between CM alone and CM+CBT in average weeks retained in treatment (overall mean=13.3 weeks) (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT)	
Treatment completion	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)		Network meta-analysis of 50 RCTs • **No difference** @ 12-week • **No difference** @ trial end. Pairwise meta-analysis • **No difference** @ 12-weeks: 3 RCTs, 421 participants; I-squared=56.8%, p=0.099: o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model) Unclear RoB **No diff bn groups**	Dropout rate (% n)

				• **No difference** @ trial end: 3 RCTs, 421 participants; I-squared=12.1%, p=0.32: ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) High RoB; Milby 2008 (Contingency managed housing alone) Unclear RoB; Rawson 2006 (n=177 CoUD/MaUD, CM alone vs Matrix Model CBT vs CM+CBT Matrix Model) Unclear RoB **No diff bn groups** Author evaluation of the quality of mixed direct and indirect evidence @ trial end • Confidence in trial end estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Outcome Importance: Important					
Sexual risk-taking behavior	Low	RCT: Shoptaw 2005[9] (Supplemental)		**No difference** between CM alone and CM+CBT groups; equivalent declines in self-reported sexual risk-taking behaviors including incidence of unprotected anal intercourse and number of prior 30-day sexual partners (n=162 MaUD MSM, CM alone vs Matrix Model CBT vs CM+Matrix Model CBT vs GCBT)	

CM+Matrix Model CBT vs CM

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Continuous stimulant abstinence	Critical	Low	RCT: Rawson 2006[6] (Supplemental) n=177 CoUD/MaUD	**No difference** between CM+Matrix Model CBT and CM alone in % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial	
			RCT: Shoptaw 2005[9] (Supplemental) n=162 MaUD MSM	**No difference** between CM+Matrix Model CBT and CM alone in longest period (in weeks) of consecutive MA metabolite-negative samples during the trial	
Stimulant abstinence	Critical	Low	RCT: Rawson 2006[6] (Supplemental) n=177 CoUD/MaUD	**No difference** between CM+Matrix Model CBT and CM alone in the number of stimulant-negative urine samples collected during the trial **No difference** between groups in % stimulant-negative urine samples collected at 17-, 26- & 52-week follow-up.	
			RCT: Shoptaw 2005[9] (Supplemental) n=162 MaUD MSM	**No difference** between CM+Matrix Model CBT and CM alone rate of stimulant abstinence during the trial **No difference** between groups at 6- or 12-mo follow-up	
Duration of treatment	Critical		RCT: Rawson 2006[6] (Supplemental) n=177 CoUD/MaUD	**No difference** between CM+Matrix Model CBT and CM alone in weeks in treatment	

			RCT: Shoptaw 2005[9] (Supplemental) n=162 MaUD MSM	**No difference** between CM+Matrix Model CBT and CM alone in weeks in treatment	
Treatment completion	Critical		RCT: Rawson 2006[6] (Supplemental) n=177 CoUD/MaUD	**No difference** between CM+Matrix Model CBT and CM alone in % of participants completing treatment	
Risky behavior	Important		RCT: Shoptaw 2005[9] (Supplemental) n=162 MaUD MSM	**No difference** between CM+Matrix Model CBT and CM alone. Across groups, overall reduction in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners @ end of treatment, 6-, and 12-month follow-ups.	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

CM+CRA vs CM

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	• **No difference** in longest duration of cocaine/meth abstinence at trial end found in network meta-analysis of 50 RCTs. • Pairwise meta-analysis: No studies	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
Stimulant abstinence rate	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 50 RCTs: • **No difference** @ 12 weeks • **No difference** @ treatment end. • **CM+CRA > CM alone** @ furthest follow-up: OR (95% CI) = 0.36 (0.16, 0.8), p=n.r. Pairwise meta-analysis • **CM+CRA > CM alone** @ 12 weeks: 1 RCT, n=100, OR (95% CI) = 3.32 (1.39, 7.9), p=n.r. ○ Higgins 2003 (n=100 CoUD, CM+CRA vs CM alone) 78% vs 51% @ 12 weeks (active voucher phase) Unclear RoB • **No difference** @ treatment end: 1 RCT, n=100	Overall cocaine/meth abstinence rate (% UDS-) Provides direct statement CM+CRA superior to CM at longest f/u after treatment completion. However, based

			○ Higgins 2003 (n=100 CoUD, CM+CRA vs CM alone) @ 24 weeks (recommended treatment duration) Unclear RoB • **CM+CRA > CM alone** @ furthest follow-up: 1 RCT, 100 participants: OR (95% CI) = 2.62 (1.09, 6.25), p=n.r. ○ Higgins 2003 (n=100 CoUD, CM+CRA vs CM alone) Unclear RoB Author evaluation of the quality of mixed direct and indirect evidence @ trial end • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	on inclusion of a single study.
Treatment retention	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 50 RCTs: • **CM+CRA > CM** @ 12 weeks: OR (95% CI) = 0.36 (0.18, 0.72), p=n.r. • **CM+CRA > CM** @ treatment end: OR (95% CI) = 0.39 (0.21, 0.71), p=0.002. Pairwise meta-analysis: • **CM+CRA > CM** @ 12 weeks: 1 RCT, n=100, OR (95% CI) = 0.2 (0.08, 0.51), p=n.r. ○ Higgins 2003 (n=100 CoUD, CM+CRA vs CM alone) 84% vs 51% @ 12 weeks (active voucher phase) Unclear RoB • **CM+CRA > CM** @ treatment end: 1 RCT, n=100, OR (95% CI) = 0.26 (0.11, 0.6), p=n.r. ○ Higgins 2003 (n=100 CoUD, CM+CRA vs CM alone) 65% vs 33% @ 24 weeks (recommended treatment duration) Unclear RoB Author evaluation of the quality of mixed direct and indirect evidence @ trial end • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout (% n) Based on inclusion of a single study.
Psychiatric symptom severity	Low	RCT: Higgins 2003[13] (Supplemental)	**No difference** between groups at 12 or 24 weeks in psychiatric problem composite core from the Addiction Severity Index • n=100 CoUD, CM+CRA vs CM alone	
Outcome Importance: Important				
Depressive symptoms	Low	RCT: Higgins 2003[13] (Supplemental)	• **CM+CRA > CM alone** @ 12 weeks (active voucher phase) in Beck Depression Inventory II scores for prior 30 days (F(1,126)=8.1, p=0.005) • **No difference** @ 24 weeks (the recommended amount of treatment)	Not co-occurring MDD

			• n=100 CoUD, CM+CRA vs CM alone	

CM+Other vs CM

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				

Stimulant abstinence rate	Low	Systematic review: Brown & DeFulio 2020[14] (Critically low)	"In the majority of these studies, treatment outcomes related to methamphetamine use were not improved by the addition of another treatment and one study found that it was more cost-effective to deliver standard contingency management (Zhang et al., 2018)." (Brown, 2020, p. 10).
			• CM + strengths-based case management
			  ○ Corsi 2012 (RCT, n=58 non-tx seeking MA use, CM + Strengths-based case management vs CM alone) No diff between groups; Corsi 2019 (RCT, n=253 non-tx seeking MA use, CM + Strengths-based case management vs CM alone) Less UDT-pos for those earning more money
			• CM + positive affect intervention
			  ○ Carrico 2015 (RCT, n=21 MA use MSM, 12 wks CM + Affect Regulation Treatment vs CM alone) No diff between groups in UDS+ or self-reported MA use @ 6 months	

Treatment satisfaction	Low	Systematic review: Brown & DeFulio 2020[14] (Critically low)	"**strengths-based case management + contingency management** condition rated the testing schedule more positively and barriers to attendance and participation less negatively than contingency management-only participants" (Brown, 2020). • Corsi 2012 (n=58 MA use non-tx seeking, CM+Strengths-based case management vs CM alone)	
Outcome Importance: Important				
Sexual risk-taking behavior	Low	Systematic review: Brown & DeFulio 2020[14] (Critically low)	"at the 4-month follow-up strengths-based case management + contingency management participants reported greater reductions in sex risk behaviors including any sex in the last 30 days, unprotected sex, sex under the influence, and sex for drugs or money than contingency management-only participants. However, at the 8-month follow-up the effect of treatment was reversed for sex under the influence and sex for drugs or money." Brown, 2020 • Corsi 2012 (n=58 MA use non-tx seeking, CM+Strengths-based case management vs CM alone)	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Individual Studies Table: CM-only studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Carrico 2015[15] (Supplemental)	Pilot RCT 12 weeks 6-month follow-up USA Community	(1) **CM alone**: 12 weeks of CM (standard program) (2) **CM + Positive affect intervention:** 5 individual sessions of ARTEMIS (Affect Regulation Treatment to Enhance Methamphetamine Intervention Success)	N= 21 **MA-using** MSM (48% HIV+, 48% White)	**Retention**: NSD between groups, 18 (86%) overall **Stimulant use** (UDS): NSD between groups @ any time **Stimulant use** (self-report MA use in past 30 days): NSD between groups @ any time **Sexual risk-taking behavior**: NSD in reduced condomless anal intercourse, Number of risky anal sex partners, or Number of risky anal sex partners on MA @ any time **Affect** (Differential Emotions Scale [DES; Izard, 1977]): • CM+ > CM-only: CM+ increased positive affect @ 2 months (34.9 v 32.8). • CM-only > CM+: CM-only reduced negative affect @ 2 months (14.8 v 12.8). • NSD between groups @ 3 & 6 months.	In Pantalone 2020[16], who labeled this an intervention targeting drug use and sexual risk behavior Also see Prev Edu Sex
Corsi 2012[17] (Supplemental)	Pilot RCT 17 weeks 4 & 8 month f/u USA Community	(1) **CM alone:** Voucher-based escalating value for MA-neg samples with reset (2) **CM + Strengths-based case management:** 1/wk for 17 weeks	N=58 non-treatment seeking heterosexual MA users (52% male, 90% white, 74% IDU)	**Follow-up rate:** 45/57 completed f/u interviews **Stimulant abstinence** (%samples): NSD between groups (70.2% vs. 65.7%). Sig reduction stim use overall @ month 4 (81.3% vs 40%, X2=11.57, p<0.001) and month 8 (44.4%, X2=11.64, p<0.001) follow-ups. **Non-injection drug use frequency**: NSD between groups; overall reduction in number of times injected MA in last month @ 4 (p = 0.04) & 8 months (p = 0.03). **Injection drug use frequency**: NSD between groups; overall reduction in number of times injected MA in last month @ 4 (p = 0.03) & 8 months (p = 0.048). **Needle risk behavior**: NSD between groups in needle risk behaviors; overall reduction in reusing needles @ 4 months but not sustained @ 8 months.	Out-of treatment participants

				Sexual risk-taking behavior: NSD between groups or overall @ 4 months. NSD between groups @ 8 months; overall reduction in Sex under the influence (77.1% vs 55.6%, $\chi 2$=3.86, p=0.59). **Attendance**: NSD between groups (n sessions 9.7 vs 12.7) **Treatment satisfaction** (ratings of CM 1-10, low to high): More CM+SBCM agreed that "Incentives enough to be motivating" (95.7% vs 68.2%, X^2_1= 5.81, p=0.02) and reported "no barriers" to participation (47.8% vs 18.2%, X^2_1=4.45, p=0.04) compared to CM-alone.	
Higgins 2003[13] (Supplemental)	RCT 12 wk active voucher phase, 24 wk treatment phase Outpatient	**(1) CM alone** **(2) CM + CRA** All participants received a suicide risk assessment at each urine sample collection, but other formal treatment was not provided.	N=100 (41% female) outpatient treatment-seeking adults with CoUD	**Treatment retention:** Percent of participants still in treatment • CM+CRA > CM (84% vs 51%) at 12 weeks, the active voucher phase • CM+CRA > CM (65% vs 33%) at 24 weeks, the recommended amount of treatment **Stimulant abstinence**: Percent of stimulant-negative urine samples collected • CM+CRA > CM (78% vs 51%) at 12 weeks, the active CM phase. • No difference at 24 weeks, the recommended amount of treatment **Depressive symptoms** (Not co-occurring MDD): Beck Depression Inventory II score for prior 30 days • CM+CRA > CM at 12 weeks, the active voucher phase (F(1,126)=8.1, p=0.005) • No difference between CM+CRA and CM at 24 weeks, the recommended amount of treatment **Psychiatric symptom severity**: Psychiatric problem composite core from the Addiction Severity Index • No difference between CM+CRA and CM at 12 or 24 weeks	
Menza 2010[5] (Supplemental)	RCT	**(1) CM alone:** Voucher-based rewards contingent on	127 non-treatment seeking MSM who use MA recruited via	Retention at 24 weeks was 84% **Stimulant use**: Percent of meth-positive urine samples collected	Higher MA+ UDT at baseline in CM-alone group

	12 weeks, 24-week follow-up USA Community	stimulant-negative UDT 2/week with escalating value **(2) TAU:** Referral to community resources	community advertising, STD or HIV clinic referral, or peer referral (55% HIV+, 54% prior 6 wk IDU of MA). Did not exclude participants who were receiving other substance use interventions. NSD in groups' reported use of outside treatment and support services.	• No difference during intervention (adjusted* RR=1.09; 95%CI: 0.71, 1.56) or follow-up (aRR=1.21; 95% CI: 0.95, 1.54, p = 0.11) **Sexual risk-taking behavior**: Percent self-reporting unprotected anal intercourse (UAI) with a partner of unknown or discordant HIV status (non-concordant UAI) • No difference during intervention (adjusted** RR=0.80, 95% CI 0.47–1.35) or follow-up (aRR= 0.51 [0.21, 1.25]	*Adjusted for baseline UDT and stage of change **Adjusted for HIV status, baseline prior 6-week non-concordant UAI and other substance use.
Rawson 2006[6] (Supplemental)	RCT 16 weeks 17-, 26- & 52-week follow-up Outpatient	**(1) CM alone:** Voucher-based (2) **Matrix Model CBT alone** (3) **CM+CBT Matrix Model**	N=177 (24% female) adults with CoUD (n=160) or MaUD (n=17) and active MA use during the 2-week screening period	**Continuous stimulant abstinence:** Significant treatment effect for % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial ($\chi2$=15.5, df=2,n=177, p<0.0001). • CM alone > CBT alone (60% vs 34.5%; $\chi2$=14.9, df=1,n=97p<0.0001)) • CM+CBT > CBT alone (69.5% vs 34.5%; $\chi2$=18.4, df=1, n=97, p<0.0001) • NSD between CM+CBT and CM **Stimulant abstinence**: Significant treatment effect for number of stimulant-negative urine samples collected during the trial (F=10.0, df=2, n=176, p< 0.0001). Post-hoc comparisons: • CM alone > CBT alone (M=27.6 v 15.5, p=0.0008) • CM+CBT > CBT alone (M=28.6 v 15.5, p=0.0003) • NSD between CM+CBT and CM alone **Stimulant abstinence rate**: NSD between groups in % stimulant-negative urine samples collected at 17-, 26- & 52-week follow-up.	

				Duration of treatment: Significant treatment effect on weeks in treatment (F=6.4, df=2, n=176, p<0.01), • CM > CBT alone (M=12.6 vs 9, p=0.003) • CM+CBT > CBT alone (M=12 vs 9, p=0.02) • NSD between CM+CBT and CM alone **Treatment completion:** Significantly lower % of participants completed treatment in CBT group (χ2=8.37;p<0.02). • CM alone > CBT alone (63% vs 40%) • CM+CBT > CBT alone (59% vs 40%) • NSD between CM+CBT and CM alone **Attendance** at CBT sessions • CM+CBT > CBT alone (M=26.5 v 19.0, F = 7.0, df=1, n=116, p< 0.01). **Other outcomes**: ASI	
Shoptaw 2005[9] (Supplemental); Reback 2004[18] (Supplemental)	RCT 2 week baseline period 16 weeks 6 & 12-month follow-up USA Outpatient	**(1) CM alone:** Voucher-based CM escalation w/ reset 3 UDS/wk (n=42) **(2) Matrix Model CBT alone**: Group format (n=40) **(3) CM+Matrix Model CBT** (n=40) **(4) GCBT**: Gay-Specific CBT integrating relevant cultural aspects of MA use by gay and bisexual men with Matrix Model CBT (Rawson et al., 1995). Included skills for reducing sexual risk behaviors. Group format 3 sessions/wk (n=40)	N=162 treatment-seeking MSM with MaUD (61% HIV+, 80% White). Exclusions for pre-existing medical or psychiatric conditions	**Retention:** 80% at 6 months **Duration of treatment**: Significant effect of intervention on mean weeks in treatment (CBT=8.9, CM=12, CM+CBT=13.3, GCBT=11.3; F(3,158) = 3.78, p < .02). Post-hoc analysis: • CM > CBT (M=12 vs 8.9, p < .05) • CM+CBT > CBT (M=13.3 vs 8.9, p < .05) • No difference between CM+CBT and CM alone **Attendance**: % of total possible sessions (CBT=41%, CM=32%, CBT+CM=74%, GCBT=56%). Incorporating CM with CBT significantly increased attendance at therapy sessions over standard CBT. **Continuous stimulant abstinence** (UDS): Significant effect of intervention on longest period (in weeks) of consecutive MA metabolite-negative samples during the trial (CBT=2.1, CM=5.1, CM+CBT=7, GCBT=3.5; F(3,158) = 11.08, p < .001). Post hoc comparisons showed CM and the CM+CBT conditions averaging periods of documented abstinence over twice (CM) and three times (CM+CBT) as long as CBT.	In Pantalone 2020[16] and Colfax 2010[19]

				• CM > CBT (M=5.1 vs 2.1, p < .001) • CM+CBT > CBT (M=7 vs 2.1, p < .001) • NSD between CM+CBT and CM alone • NSD between groups at 6- or 12-mo follow-up **Stimulant abstinence rate** (UDS): Significant effect of intervention on % MA-negative urine samples collected during the trial ($\chi 2$ (3) = 8.10, p < .05). Longitudinal model showed CBT provided fewer MA-neg samples than other three conditions (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; $\chi 2$ (1) = 10.03, p < .01). • CM > CBT • CM+CBT > CBT • NSD between CM+CBT and CM alone NSD between groups at 6- or 12-mo follow-up Across groups, significant reduction at the end of treatment from baseline in % UDS MA+ (48% vs 17%, McNemar's Q = 18.69, p < .0001), which was sustained at 6- and 12-month follow-ups. **Sexual risk behavior**: NSD between groups in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners at end of treatment or follow-up; significant reduction at the end of treatment in all groups for both measures, which were sustained at 6- and 12-month follow-ups.	

Other Resources

Source	Resource	Comments
CRA+CM	NIDA, Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition), Community Reinforcement Approach Plus Vouchers (Alcohol, Cocaine, Opioids) (https://www.drugabuse.gov/publications/ principles-drug-addiction-treatment-researchbased-guide-third-edition/evidence-basedapproaches-to-drug-addiction-treatment/ behavioral-therapies/community-reinforcementapproach-vouchers): This resource describes the Community Reinforcement Approach (CRA) Plus Vouchers, an intensive 24-week outpatient therapy that combines counseling, vocational services, recreational and social activities, and material incentives to help patients maintain abstinence.	
	NIDA, Motivational Incentives Package (https:// www.drugabuse.gov/nidamed-medical-healthprofessionals/ctn-dissemination-initiative/ motivational-incentives-package-proven-approachto-treatment): This NIDA webpage provides behavioral healthcare practitioners with access to motivational incentive tools for engaging clients in behavioral health therapy.	

	NIDA/SAMHSA, Motivational Incentives Suite (https://collaborativeforhealth.org/ bettertxoutcomes/): The Motivational Incentives Suite is a collection of tools and resources to help organizations understand and implement CM into practice. NIDA, Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition), **Contingency Management Interventions/ Motivational Incentives (Alcohol, Stimulants, Opioids, Marijuana, Nicotine)** (https://www.drugabuse.gov/publications/ principles-drug-addiction-treatment-researchbased-guide-third-edition/evidence-basedapproaches-to-drug-addiction-treatment/ behavioral-therapies/contingency-managementinterventions-motivational-incentives): This resource briefy summarizes how to implement two approaches to CM, Voucher-Based Reinforcement and Prize Incentives CM. **UCLA, Integrated Substance Abuse Programs, A Treatment Manual for Implementing Contingency Management** (http://www.uclaisap.org/assets/ documents/Manual%20for%20Implementing%20 Contingency%20Management_11-8-2011%20 clean.pdf): This online treatment manual describes how to implement a CM program for individuals who were recently paroled and are seeking SUD treatment in the community. **Yale University Psychotherapy Development Center, Contingency Management: Using Motivational Incentives to Improve Drug Abuse Treatment** (http://lib.adai.washington.edu/ctnlib/ PDF/CMmanual.pdf): Research on the use of CM interventions shows the effcacy of providing tangible incentives to clients who are targeting distinct behaviors on their journey to achieving recovery from SUDs. This publication provides an overview of research fndings and guides practitioners on applying CM strategies across clinical settings.	

Evidence to Decision (EtD) Table

CM vs NCR/TAU

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CM vs NCR/TAU CM consistently produced longer durations of continuous abstinence and lower rates of stimulant use than NCR and TAU. These effects were strongest during the trials, and appeared to decrease gradually over post-treatment follow-ups.	**CM vs NCR/TAU** *(Large)* The size of the desirable effects depends on the type (voucher vs cash) and magnitude of the incentive.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
None		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies

		☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
The balance of effects strongly supports CM over NCR and TAU, at least during treatment. Effects favoring CM began to diminish after treatment, but appear to persist for at least 3 months.		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
The research evidence quality is high, as it comes from several well-done meta-analyses and systematic reviews and is consistent across studies		☐ No evidence ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	The main outcomes are highly valued across different groups	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*

Higher prevalence of SUD in disadvantaged populations	Reasonable that increasing access to treatment would reduce inequity in access. CM is somewhat resource intensive interventions, given that funds to obtain incentives are needed. But the provision of this intervention to underserved populations would reduce health inequities. I would rate as "probably reduced" - agree due to lack of studies	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Resistance to the use of CM has been rapidly declining as information about its effectiveness is more broadly disseminated. However, there is still resistance in some groups to the use of CM in the treatment of substance use disorders. **CM vs NCR/TAU** (Uncertain) Resistance to the use of CM has been rapidly declining as information about its effectiveness is more broadly disseminated. However, there is still resistance in some groups to the use of CM in the treatment of substance use disorders. Anecdotal evidence that acceptance of CM in the field is lower than expected. EtD studies do not address this directly; would expect key stakeholders would accept	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
CM was successfully implemented in the VA using vouchers, although the VA is a unique case.	CM does require funds to obtain incentives. There are examples of creative ways to secure funds, but there are still many settings where this is not currently possible. Legality of adequate reimbursements > $75/year is undetermined. May vary depending on the reimbursement method and health care system (eg, VA vs Medicare vs private health insurance).	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

CM vs Other

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*

CM Alone: Moderate Shoptaw 2005[9] **CM vs CBT vs CM+CBT** vs GCBT Population: 162 outpatient treatment-seeking MSM with MUD; Outcome: Longest period (in weeks) of consecutive meth metabolite-negative samples during the trial; CM > CBT (m=5.1 vs 2.1 respectively); treatment retention: CM > CBT (m=12 vs 8.9 weeks respectively); no diff abstinence. Rawson 2006[6] **CM vs CBT vs CM+CBT** Population: 177 (24% female) adults with active meth use during the 2-week screening period, outpatient setting Outcome: Percentage of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial**;** CM ≥ CBT (60% vs 34.5%); treatment retention: CM > CBT (m=12 v 9); no diff abstinence. **CM vs CBT**: Large Research findings consistently demonstrate that CM produces longer periods of continuous abstinence from stimulants and less stimulant use than CBT during treatment. **CM vs CRA:** None **CM vs Other/CRA**: Small Very few direct comparisons between CM and CRA, TSF, Meditation, and Supportive-Expressive treatments were identified. Using other techniques to compare these interventions, a meta-analysis found few differences between CM and these other interventions. CM produced longer durations of continuous abstinence than CRA, longer retention than TSF, and higher abstinence rates than Supportive-Expressive	**CM Alone**: Moderate Higgins et al. 2003 does not support efficacy vs. CM+CRA; Menza et al. 2010; neg result CM vs referral (use; sexual risk); Brown & DeFullio 2020 CM+SBCM more acetated than CM alone, less sec risk; Corsi et al. 2012; CM+SBCM better for submitting urines and neg urines; Carrico et al. 2015, very small study n<15 each. NB: older studies by Higgins, Petry, Silverman (1996 – 2003) support efficacy of CM vs other txs. These were not reviewed. **CM vs Other/CRA**: Small Lack of direct comparisons between interventions reduces the strength of these findings **CM+CBT vs CM** *(Moderate)* Brown&FeFullio 2020 (quality critically low): Shoptaw et al. 2005 – decreased risky sexual behavior; Reback&Shoptaw 214, reduced # male sexual partners **CM+CRA vs CM** *(Moderate)* All the evidence is based upon a single well-conducted RTC that included only participants with cocaine use disorder; thus, nothing can be concluded about this comparison for methamphetamine use disorder. Although the odds ratios are fairly substantial, it would be unwise to make a judgment of large based upon a single trial. **CM+Other vs CM**: No rating Menza et al. 2010; neg result CM vs referral (use; sexual risk); Brown & DeFullio 2020 CM+SBCM more acetated than CM alone, less sec risk; Corsi et al. 2012; CM+SBCM better for submitting urines and neg urines; Carrico et al. 2015, very small study n<15 each.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know

therapy during treatment, but lower rates of abstinence than CRA at final follow-up. **CM+CBT vs CM** DeCrescenzo 2018[1]: CM vs CM+CBT: n diff. tx retention, abstinence, dropout. Farronato 2013[8]: summarizes support (McKay2010 and Epstein 2003; no effect Rawson 2002, 2006 or Rowan-Szal 2005. 2017). DeGiorgi 2018[11] cites Glasner-Edwards 2017[12] favors CM+MBi OR 0.78 **CM+CRA vs CM** For some endpoints (stimulant use and treatment retention) the evidence favors CM + CRA vs CM alone. Higgins 2003[13] showed improvements on a number of outcomes. CRA had slightly better long-term outcomes in regard to cocaine use than does CM.		
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CM vs NCR/TAU: None CM vs CBT: None CM vs CRA: no undesirable effects **CM vs Other/CRA**:None Randomized trials do not show any undesirable effects of CM. **CM+CRA vs CM** There do not appear to be any undesirable effects of these interventions.	**CM Alone**: Don't know Undesirable effects of CM not expected; Unaware of financial analysis arguing adverse effect. **CM+CBT vs CM:** None, Don't know Undesirable effects of CM o CBT not expected; Unaware of financial analysis arguing adverse effect. **CM+CRA vs CM** *(None)*	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Balance of effects strongly favor CM. CM vs CBT: Substantially favors	**CM Alone**: Don't know Financial costs vs. effects difficult to ascertain, since rates of reimbursement vary between studies.	☒ Substantially favors intervention

The balance of effects strongly supports CM over CBT, at least during treatment. Effects favoring CM are no longer present at last follow-up. CM vs CRA: Favors intervention **CM vs Other/CRA**: *Somewhat favors intervention* There is a small advantage to the intervention.	**CM+CBT vs CM:** Don't know Financial costs vs. effects difficult to ascertain, since rates of reimbursement vary between studies. I would probably say favors neither, that is adding CBT to CM does not produce better outcomes than CM alone. Agree **CM+CRA vs CM:** Somewhat favors intervention Since there are no undesirable effects the balance slightly favors the combined intervention CM+CRA.	☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
CM Alone: Low See desirable effects **CM vs CBT**: High The research evidence quality is high, as it comes from several well-done meta-analyses and systematic reviews and is consistent across studies CM vs CRA: Same as above. **CM vs Other/CRA**: Low Low, due to lack of direct comparisons between CM and the other interventions **CM+CBT vs CM** See desirable effects **CM+CRA vs CM**	**CM Alone**: Low 2 larger positive results; neg results smaller studies, or with less critical outcomes; older lit not reviewed. **CM vs CRA**: None **CM+CBT vs CM:** Moderate De Crescenzo highest quality Overall moderate certainty CM+CBT no better than CM alone **CM+CRA vs CM:** Low All the evidence is based upon one single site (though well conducted) RCT. (Low)	☐ No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
CM+CRA vs CM	**CM Alone**: Probably no	☐ Yes

No direct evidence found in systematic review.	**CM vs CBT**: No The main outcomes are highly valued across different groups **CM vs CRA**: **CM vs Other/CRA**: No The main outcomes are highly valued across different groups **CM+CBT vs CM:** Probably no **CM+CRA vs CM:** No No unexpected uncertainty about value stakeholders place in the outcome.	☐ Possibly yes ☐ Probably no ☒ No
* **Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
CM+CRA vs CM: Probably reduced No direct evidence found in systematic review. **CBT:** Wider use of CBT in underfunded populations would likely reduce health inequities, as it appears to be superior to TAU.	**CM Alone**: Uncertain Unaware of direct studies, not examined here; common sense would argue if minoritized communities have greater harm from StUD, successful treatment should reduce health inequity, but remains to be demonstrated. **CM vs CBT:** Probably reduced Common sense would argue if minoritized communities have greater harm from StUD, successful treatment should reduce health inequity, but remains to be demonstrated. Both CM and CBT are somewhat resource intensive interventions, given that incentives are needed for the former and the availability of highly trained therapists is needed for the latter. But the provision of these interventions to underserved populations would reduce health inequities. **CM vs CRA**: **CM vs Other/CRA**: Reduced CM and the comparison conditions are resource intensive interventions, given that incentives are needed for the CM and the availability of highly trained therapists is needed for the other interventions. But the provision of these interventions to underserved populations would reduce health inequities. **CM+CBT vs CM:** Uncertain	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies

	Unaware of direct studies, not examined here; common sense would argue if minoritized communities have greater harm from StUD, successful treatment should reduce health inequity, but remains to be demonstrated. **CM+CRA vs CM:** Probably reduced If treatment is effective, it should benefit those more adversely affected, and so reduce disparities. Due to lack of direct evidence, will say probably. Also, research priority should be evaluating cultural appropriateness for specific minority populations.	
* **Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT: CBT is acceptable to all stakeholders.	**CM Alone**: Probably yes Anecdotal evidence that acceptance of CM in the field is lower than expected. EtD studies do not address this directly; would expect key stakeholders would accept **CM vs CBT:** Probably yes Resistance to the use of CM has been rapidly declining as information about its effectiveness is more broadly disseminated. However, there is still resistance in some groups to the use of CM in the treatment of substance use disorders. Anecdotal evidence that acceptance of CM in the field is lower than expected. EtD studies do not address this directly; would expect key stakeholders would accept. **CM vs CRA:** It would have to be studied for methamphetamine use disorder before it is applied widely to treat people with that disorder. At the present time it does not appear feasible to implement CRA widely. It would be necessary to train the workforce and assure it can be paid for. CRA requires more resources than CBT or TAU. Only an economic analysis could inform us as to whether it is really cost-effective compared to other treatments. Unknown if it could be widely implemented given extensive program resource requirements. **CM vs Other/CRA:** Uncertain Resistance to the use of CM has been rapidly declining as information about its effectiveness is more broadly disseminated. However, there is still resistance in some groups to the use of CM in the treatment of substance use disorders. **CM+CBT vs CM: Probably yes**	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

	Anecdotal evidence that acceptance of CM in the field is lower than expected. EtD studies do not address this directly; would expect key stakeholders would accept **CM+CRA vs CM: Uncertain** CRA is a complicated intervention to deliver and some patients may not want such a comprehensive intervention. Some providers are resistant to CM.	
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT: The fact that CBT can be delivered in group sessions makes it more feasible for many programs. **CM+CRA vs CM** No direct evidence found in systematic review.	**CM:** **CM Alone: Uncertain** Individual practitioner providers may have difficulty incorporating CM into practice; most groups, given an internal champion and training could provide CM but significant inertia to doing so in a busy practice **CM vs CBT: Varies** Individual practitioner providers may have difficulty incorporating CM into practice; most groups, given an internal champion and training could provide CM but significant inertia to doing so in a busy practice. CM does require funds to obtain incentives. There are examples of creative ways to secure funds, but there are still many settings where this is not currently possible. **CM vs CRA**: It would have to be studied for methamphetamine use disorder before it is applied widely to treat people with that disorder. At the present time it does not appear feasible to implement CRA widely. It would be necessary to train the workforce and assure it can be paid for. CRA requires more resources than CBT or TAU. Only an economic analysis could inform us as to whether it is really cost-effective compared to other treatments. Unknown if it could be widely implemented given extensive program resource requirements. **CM vs Other/CRA: Uncertain** CM does require funds to obtain incentives. There are examples of creative ways to secure funds, but there are still many settings where this is not currently possible. The other interventions all require highly trained therapists, and are usually delivered in individual rather than group sessions, which can make them not feasible in current SUD treatment programs	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

	CM+CBT vs CM: Uncertain Individual practitioner providers may have difficulty incorporating CM into practice; most groups, given an internal champion and training could provide CM but significant inertia to doing so in a busy practice **CM+CRA vs CM: Uncertain/Varies** Very few settings have the resources or trained staff to implement CRA. Funding for CM can be challenging to obtain.	

Conclusions

Justification

There is strong evidence that contingency management is an effective intervention for increasing treatment engagement and reducing of stimulant use. The CGC understands that there are barriers to implementing contingency management including the financial cost of programs, regulatory barriers, and conflict among those ambivalent about "rewarding drug use." However, Contingency Management has the best effectiveness in the treatment of stimulant use disorders compared to any other intervention.

Subgroup Considerations

None known.

Implementation Considerations

Effective operation of Contingency Management requires:

- Funding, training, capacity to obtain point of care toxicology testing, and at present at least twice weekly clinic attendance.

Methods and processes of Contingency Management should consider the following factors:

- Use clinically effective amounts for the contingency rewards within the context of current regulations.

Research Priorities

1. Determining optimal amounts of rewards for methamphetamine abstinence
2. Studying best practices in implementation and sustainment.

References

1. De Crescenzo F, Ciabattini M, D'Alò GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. Degenhardt L, ed. *PLoS Med*. 2018;15(12):e1002715. doi:10.1371/journal.pmed.1002715
2. Minozzi S, Saulle R, De Crescenzo F, Amato L. Psychosocial interventions for psychostimulant misuse. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 29, 2016. doi:10.1002/14651858.CD011866.pub2
3. Sayegh CS, Huey SJ, Zara EJ, Jhaveri K. Follow-up treatment effects of contingency management and motivational interviewing on substance use: A meta-analysis. *Psychol Addict Behav*. 2017;31(4):403-414. doi:10.1037/adb0000277

4. Ginley MK, Pfund RA, Rash CJ, Zajac K. Long-term efficacy of contingency management treatment based on objective indicators of abstinence from illicit substance use up to 1 year following treatment: A meta-analysis. *J Consult Clin Psychol*. 2021;89(1):58.
5. Menza TW, Jameson DR, Hughes JP, Colfax GN, Shoptaw S, Golden MR. Contingency management to reduce methamphetamine use and sexual risk among men who have sex with men: a randomized controlled trial. *BMC Public Health*. 2010;10(1):774. doi:10.1186/1471-2458-10-774
6. Rawson RA, McCann MJ, Flammino F, et al. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. *Addiction*. 2006;101(2):267-274. doi:10.1111/j.1360-0443.2006.01312.x
7. AshaRani PV, Hombali A, Seow E, Ong WJ, Tan JH, Subramaniam M. Non-pharmacological interventions for methamphetamine use disorder: a systematic review. *Drug Alcohol Depend*. 2020;212:108060. doi:10.1016/j.drugalcdep.2020.108060
8. Farronato NS, Dürsteler-Macfarland KM, Wiesbeck GA, Petitjean SA. A systematic review comparing cognitive-behavioral therapy and contingency management for cocaine dependence. *J Addict Dis*. 2013;32(3):274-287. doi:10.1080/10550887.2013.824328
9. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134. doi:10.1016/j.drugalcdep.2004.10.004
10. Bentzley BS, Han SS, Neuner S, Humphreys K, Kampman KM, Halpern CH. Comparison of Treatments for Cocaine Use Disorder Among Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2021;4(5):e218049. doi:10/gjw4ck
11. De Giorgi R, Cassar C, Loreto D'alò G, et al. Psychosocial interventions in stimulant use disorders: a systematic review and qualitative synthesis of randomized controlled trials. *Riv Psichiatr*. 2018;53(5):233-255. doi:10.1708/3000.30003
12. Glasner S, Mooney LJ, Ang A, et al. Mindfulness-Based Relapse Prevention for Stimulant Dependent Adults: A Pilot Randomized Clinical Trial. *Mindfulness (N Y)*. 2017;8(1):126-135. doi:10.1007/s12671-016-0586-9
13. Higgins ST, Sigmon SC, Wong CJ, et al. Community Reinforcement Therapy for Cocaine-Dependent Outpatients. *Archives of General Psychiatry*. 2003;60(10):1043-1052. doi:10.1001/archpsyc.60.9.1043
14. Brown HD, DeFulio A. Contingency management for the treatment of methamphetamine use disorder: A systematic review. Drug Alcohol Depend. 2020;216:108307. https://doi.org/10.1016/j.drugalcdep.2020.108307
15. Carrico AW, Nation A, Gómez W, et al. Pilot trial of an expressive writing intervention with HIV-positive methamphetamine-using men who have sex with men. *Psychol Addict Behav*. 2015;29(2):277-282. doi:10.1037/adb0000031
16. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
17. Corsi KF, Lehman WE, Min SJ, et al. The Feasibility of Interventions to Reduce HIV Risk and Drug Use among Heterosexual Methamphetamine Users. *J AIDS Clin Res*. 2012;Suppl 1(10):6953. doi:10.4172/2155-6113.S1-010
18. Reback CJ, Larkins S, Shoptaw S. Changes in the Meaning of Sexual Risk Behaviors Among Gay and Bisexual Male Methamphetamine Abusers Before and After Drug Treatment. *AIDS Behav*. 2004;8(1):87-98. doi:10/dkk7p8
19. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *Lancet*. 2010;376(9739):458-474. doi:10.1016/S0140-6736(10)60753-2

Table 2. Community Reinforcement Approach

Recommendation: The following three interventions have the most supportive evidence and are preferred alongside contingency management: **Community Reinforcement Approach (CRA)**, CBT, and the Matrix Model.

Clinical Question Summary Table

Clinical Question	1. Is CRA (with or without background treatment) an effective and appropriate treatment for StUD? 2. Is CRA more effective than other behavioral treatments for StUD? 3. Does adding Contingency Management to CRA improve outcomes for StUD? 4. What additional considerations and implementation strategies may influence the effects of CRA?
Population	Patients being treated for stimulant use disorder in the early phase of treatment
Intervention	Community Reinforcement Approach (CRA) with or without additional treatment
Comparison	Treatment as usual or Other behavioral treatment
Main Outcomes	Stimulant abstinence, stimulant use, treatment retention
Setting	Inpatient or outpatient SUD treatment
Background & Definitions	Notes • See De Giorgi 2018[1] for intervention descriptions
Abbreviations	**CBT:** Cognitive behavioral therapy, **CM:** Contingency management, **CRA:** Community reinforcement approach, **MA:** Methamphetamine, **OR:** Odds ratio, **TAU:** Treatment as usual, **UDS:** Urine drug screen
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

CRA vs TAU

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on longest duration (in weeks) of cocaine/MA abstinence (UDS) in a network meta-analysis of 25 RCTs No studies found for pairwise analysis.	

Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 42 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 46 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Study limitations = RoB 33% low, 25% unclear, 42% high = 2.09 or 0.09
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** CRA > TAU cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 32 RCTs: OR (95% CI) = 2.71 (1.12, 6.54), p=n.r. No studies found for pairwise analysis.	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on dropout rate (%n) in a network meta-analysis of 41 RCTs No studies found for pairwise analysis.	
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** CRA had higher retention in a network meta-analysis of 43 RCTs: OR (95% CI) = 2.77 (1.38, 5.58), p=0.004. • 4 patients needed to be treated with community reinforcement approach to have 1 fewer patient dropping out at the end of treatment compared to TAU (NNT=4.02 (95% CI 2.58–12.62) No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CRA vs CM

Outcome	Strength of Evidence[i]	Evidence (Quality[ii])	Effect/Impact	Comments

Critically Important Outcomes				
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CM:** CM had a longer longest duration (in weeks) of cocaine/MA abstinence (UDS-) compared to CRA in a network meta-analysis of 25 RCTs: SMD (95% CI) = 0.82 (0.06, 1.59), p=n.r. No studies found for pairwise analysis.	
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 42 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 46 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** CRA > CM on cocaine/MA abstinence rate (%n UDS-) in a network meta-analysis of 32 RCTs: OR (95% CI) = 0.41 (0.17, 0.97), p=n.r. No studies found for pairwise analysis.	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Dropout rate (%n) in a network meta-analysis of 41 RCTs No studies found for pairwise analysis.	
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Dropout rate (%n) in a network meta-analysis of 43 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence at trial end • Confidence in estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

CRA+CM vs CRA

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
			No effect in network meta-analysis of 21 RCTs	

Continuous stimulant abstinence @ 12 weeks		Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CM:** CM+CRA > CRA: SMD (95% CI) = 0.72 (0.07, 1.36), p=n.r. Based on pairwise meta-analysis: 1 RCT, n=40 • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation)**	Longest duration (weeks) of cocaine/MA abstinence (UDS-)
Continuous stimulant abstinence @ trial end	Very low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CM:** CM+CRA > CRA: SMD (95% CI) = 0.81 (0.35, 1.26), p=n.r. Based on network meta-analysis of 25 RCTs **Positive for CM**: CM+CRA > CRA: SMD (95% CI) = 0.82 (0.49, 1.15), p=n.r.; no between study heterogeneity I^2=0% Based on pairwise meta-analysis: 2 RCTs, n=158 • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation);** Secades-Villa 2013 (n=118 CoUD, 24 wks CRA+CM vs CRA) **High RoB** mean (SD)= 3.1 (2.4) vs 1.9 (2.5), t=2.6, df=116, p=0.01	Longest duration (in weeks) of cocaine/MA abstinence (UDS-)
Stimulant abstinence @ 12 weeks	Very low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CM:** CM+CRA > CRA: OR (95% CI) = 4.3 (1.01, 18.24), p=n.r. Based on network meta-analysis of 42 RCTs **Positive for CM:** CM+CRA > CRA: OR (95% CI) = 4.29 (1.42, 12.99), p=n.r. Based on pairwise meta-analysis: 1 RCT, n=58 • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **High RoB**	Cocaine/MA abstinence rate (%n UDS-)
Stimulant abstinence @ trial end	Very low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** network meta-analysis of 46 RCTs **No effect:** pairwise meta-analysis: 2 RCTs, n=98. No significant between study heterogeneity I^2=16.1%, p=0.275 • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **High RoB;** Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation)** CM+CRA > CRA @ 12 wks Author evaluation of the quality of mixed direct and indirect evidence: • Confidence in estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Cocaine/MA abstinence rate (%n UDS-)
		Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for CM:** CM+CRA > CRA in cocaine abstinence rate in 4 RCTs (5 publications) • Garcia-Fernandez 2011a & 2011b (n=58 CoUD Spain, 6 mo CRA+CM vs CRA) Mixed. Higher mean % UDS- samples during treatment (m[sd] =	All CoUD Slightly different results reported in Garcia-Fernandez

			97.07 [6.3] vs 79.76 [25.8], t=3.50, df=31.405, p=0.001, effect-size correlation $r_{Y\lambda}$ =0.41), but NSD in %UDS- point-prevalence @ 6 months (65.5% vs 44.8%); Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA @ 12 wks ; Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) UDT% CM>NCR @ 24 wks; Secades-Villa 2013 (n=118 CoUD, 24 wks CRA+CM vs CRA) CM+CRA > CRA in longest duration of cocaine abstinence (months) (mean(SD)= 3.1 (2.4) vs 1.9 (2.5), t=2.6, df=116, p=0.01).	2011b: CRA+CM (mean = 95.7, SD = 7.2) vs CRA (mean = 79.3, SD = 25.7; t(32.46) = 3.30, p = 0.002, $r_{Y\lambda}$ = 0.39).
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** network meta-analysis of 32 RCTs	Cocaine/MA abstinence rate (%n UDS-)
			No effect: pairwise meta-analysis: 2 RCTs, n=98. no between study heterogeneity I^2=0%. • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **High RoB;** Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation)** CM+CRA > CRA @ 24 wks	
		Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for CM:** CM+CRA > CRA in cocaine abstinence rate in 4 RCTs (5 publications) • Garcia-Fernandez 2011a & 2011b (n=58 CoUD Spain, 6 mo CRA+CM vs CRA) NSD @ 12 months (58.6% vs 37.9%, n=58, χ^2=1.72, df=1, p=0.18); Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA @ 24 wks; Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) self-report CM>NCR during follow-up months 6-18 (19% vs 6%)	All CoUD
Time in treatment	Moderate	Systematic review: De Giorgi 2018[1] (Moderate)	**Mixed** evidence for weeks retained in treatment **1 equivocal** (2 publications of 1 RCT) • Garcia-Fernandez 2011a & 2011b (n=58 CoUD, CRA+CM vs CRA) NSD @ 6 months (m[sd]=19.2 [7.6] vs 17.03 [9.2]) or @ 12 months (m[sd]=35.7 [18.5] vs 28.9 [19.9], t=1.35, df=56, p=0.18) **2 positive for CM** (2 RCT)**:** • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA @ 24 weeks; Secades-Villa 2013 (n=118 CoUD, 24 wks CRA+CM vs CRA) CM+CRA > CRA @ 24 weeks (mean (sd)=18.1 (8.7) vs 14.2 (10.0), t=2.3, df=112.9, p=0.02)	All CoUD
	Very low		**No effect:** network meta-analysis of 41 RCTs	Dropout (%n)

Treatment retention @ 12 weeks		Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CM:** CM+CRA > CRA in pairwise meta-analysis: 2 RCTs, n=98, OR (95% CI) = 0.37 (0.14, 0.99), p=n.r. No between study heterogeneity I^2=0% • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **High RoB** NSD; Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation)** CM+CRA > CRA	
		Systematic review: De Giorgi 2018[1] (Moderate)	**Mixed** evidence of effects on retention (%n) @ 12 weeks **1 equivocal** (1 RCT)**:** • Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) NSD **1 positive for CM** (1 RCT)**:** • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA	Retention (%n)
Treatment retention @ trial end	Very low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** network meta-analysis of 43 RCTs	Dropout (%n)
			No effect: pairwise meta-analysis (3 RCTs, n=216). Significant between study heterogeneity (I^2=71%, p=0.033). • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **High RoB** NSD; Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) **Unclear RoB (randomization, allocation)** CM+CRA > CRA; Secades-Villa 2013 (n=118 CoUD, CRA+CM vs CRA) **High RoB**	
			Author evaluation of the quality of mixed evidence at trial end • Confidence in estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Systematic review: De Giorgi 2018[1] (Moderate)	**Mixed** evidence of effects on retention (%n) @ 24 weeks **2 equivocal** (2 RCTs): • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) **NSD;** Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) **NSD** **1 positive for CM** (1 RCT)**:** • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA	Retention (%n)
Important Outcomes				
Psychosocial functioning @ 24 weeks	N/A	Systematic review: De Giorgi 2018[1] (Moderate)	**No effect** in 3 RCTs on ASI Psychiatric sub-scale improvements • Garcia-Fernandez 2011a; Garcia-Fernandez 2011b (n=58 CoUD, CRA+CM vs CRA) NSD @ Bonferroni correction level (α=0.0023) (0.08 ± 0.11 vs 0.19 ± 0.20, t= -2.05, df=26,9, p=0.04, effect-size correlation $r_{Y\lambda}$= -0.07);	ASI=Addiction Severity Index

			Higgins 1994 (n=40 CoUD, CRA+CM vs CRA); Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) NSD	
Psychosocial functioning @ 12 months	N/A	Systematic review: De Giorgi 2018[1] (Moderate)	**No effect** in 1 RCT on ASI Psychiatric sub-scale improvements • Garcia-Fernandez 2011a; Garcia-Fernandez 2011b (n=58 CoUD, CRA+CM vs CRA) NSD	
Drug use severity @ 24 weeks	N/A	Systematic review: De Giorgi 2018[1] (Moderate)	**Mixed evidence** on improvements in the ASI Drug sub-scale **1 positive effects** (1 RCT) • Higgins 1994 (n=40 CoUD, CRA+CM vs CRA) CM+CRA > CRA **2 equivocal** (2 RCTs) • Garcia-Fernandez 2011a (n=58 CoUD, CRA+CM vs CRA) NSD; Higgins 2000 (n=70 CoUD, CRA+CM vs CRA+NCR) NSD	
Drug use severity @ 12 months	N/A	Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for** improvements in the ASI Drug sub-scale in 1 RCT • Garcia-Fernandez 2011b (n=58 CoUD, CRA+CM vs CRA) **CM+CRA > CRA** (0.00 ± 0.10 0.06 ± 0.09, n=34, Mann-Whitney U= -2.71, p=0.00)	

CRA vs CBT

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on longest duration (weeks) of cocaine/MA abstinence (UDS-) in a network meta-analysis of 25 RCTs. No studies found for pairwise analysis.	
Continuous stimulant abstinence during follow-up	Low	Systematic review: De Giorgi 2018[1] (Moderate)	**No effect** on self-reported cocaine/MA abstinence during the follow-up period: 1 RCT, n=82 **1 no effect** (2 publications on same data-set): • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) High RoB (attrition) Self-report cocaine use	
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on cocaine/MA abstinence rate (% UDS-) in a network meta-analysis of 42 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Very low		**No effect** on cocaine/MA abstinence rate (% UDS-) in a network meta-analysis of 46 RCTs	

		Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on cocaine/MA abstinence rate (% UDS-) in a pairwise meta-analysis: 1 RCT, n=74 **1 no effect** (2 publications on same data-set): • Sanchez-Hervas 2010; Secades-Villa 2011 (n=82 CoUD in Spain, 24 wks CRA vs TAU [CBT w/out protocol]) **High RoB**	
			Author evaluation of the quality of mixed evidence at trial end • Confidence in estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA**: CRA had a higher stimulant abstinence rate (%n UDS-) compared to CBT in a network meta-analysis of 32 RCTs: OR (95% CI) = 0.39 (0.17, 0.91), p=n.r.	
			Positive for CRA: CRA had a higher stimulant abstinence rate (%n UDS-) compared to CBT in a pairwise meta-analysis: 1 RCT, n=74, OR (95% CI) = 2.77 (1.04, 7.41), p=n.r. **1 positive for CRA** (2 publications on same data-set): • Sanchez-Hervas 2010; Secades-Villa 2011 (n=82 CoUD in Spain, 24 wks CRA vs TAU [CBT w/out protocol]) **High RoB** @ 12 mo	
		Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for CRA**: CRA > TAU in cocaine abstinence rate (%n UDS-): 1 RCT, n=82 **1 mixed effect** (2 publications on same data-set): (1 RCT) • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) CRA>TAU in completers-only analysis (95% vs 69%). NSD @ 12 months in ITT analysis assuming missing-positive	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on dropout rate (%n) in a network meta-analysis of 41 RCTs	
Treatment retention @ trial end	Very low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect** on dropout rate (%n) in a network meta-analysis of 43 RCTs	
			No effect on dropout rate (%n) in a pairwise meta-analysis: 1 RCT, n=74: **1 no effect** (2 publications on same data-set): • Sanchez-Hervas 2008; Secades-Villa 2011 (n=82 CoUD in Spain, 24 wks CRA vs TAU [CBT w/out protocol]) **High RoB**	
			Author evaluation of the quality of mixed evidence at trial end	

			• Confidence in estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for CRA**: CRA had higher retention rate (%n): 1 RCT, n=82, 55% vs 40% **1 no effect** (2 publications on same data-set): • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, CRA vs TAU [CBT w/out protocol]) NSD @ 24 wks	
Important Outcomes				
Psychosocial functioning @ 12 months	N/A	Systematic review: De Giorgi 2018[1] (Moderate)	**Positive for CRA**: CRA had greater improvements in ASI composite scores: 1 RCT, n=82 **1 positive effect** (2 publications on same data-set): • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) CRA>TAU in Alcohol and Family/social composite	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CRA+CM vs CBT+CM

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No difference** in network meta-analysis of 25 RCTs. No studies found for pairwise analysis.	Longest duration of cocaine/MA abstinence (weeks)
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 42 RCTs: OR (95% CI) = 0.4 (0.17, 0.92), p=n.r. No studies found for pairwise analysis.	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No difference** in network meta-analysis of 46 RCTs. No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence	Cocaine/MA abstinence rate (% UDS-)

			• Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 32 RCTs: OR (95% CI) = 0.4 (0.17, 0.98), p=n.r. No studies for pairwise analysis.	Cocaine/MA abstinence rate (% UDS-)
Treatment retention@ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No difference** in network meta-analysis of 41 RCTs. No studies found for pairwise analysis.	Dropout rate (%n)
Treatment retention@ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 43 RCTs: OR (95% CI) = 0.39 (0.19, 0.79), p=0.009. No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)

CRA vs Supportive Expressive Psychodynamic Therapy (SEPT)

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (% UDS-) in network meta-analysis of 42 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (% UDS-) in network meta-analysis of 46 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** CRA had higher cocaine/MA abstinence rates (%n UDS-) compared to SEPT: OR (95% CI) = 3.03 (1.09, 8.41), p=n.r. based on network meta-analysis of 32 RCTs	

			No studies found for pairwise analysis.	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Dropout rate (%n) in network meta-analysis of 41 RCTs No studies found for pairwise analysis.	
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** MBT had a higher dropout rate (%n) compared to CRA in a network meta-analysis of 43 RCTs: OR (95% CI) = 3.17 (1.19, 8.43), p=0.02 No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

[i]: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CRA vs Twelve Step Facilitation (TSF)

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant abstinence @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (% UDS-) in network meta-analysis of 42 RCTs No studies found for pairwise analysis.	
Stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Cocaine/MA abstinence rate (% UDS-) in network meta-analysis of46 RCTs No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

Stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** CRA had higher cocaine/MA abstinence rates (%n UDS-) compared to TSF in a network meta-analysis of 32 RCTs: OR (95% CI) = 3.17 (1.24, 8.08), p=n.r. No studies found for pairwise analysis.	
Treatment retention @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[2] (High)	**No effect:** Dropout rate (%n) in network meta-analysis of 41 RCTs No studies found for pairwise analysis. Evidence of significant local incoherence from the side-splitting model	
Treatment retention @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[2] (High)	**Positive for CRA:** TSF had a higher dropout rate (%n) compared to CRA in a network meta-analysis of 43 RCTs: OR (95% CI) = 3.42 (1.55, 7.55), p=0.002 No studies found for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Moderate; Study limitations: some concerns; Imprecision: no concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Higgins 2003[3] (Supplemental)	RCT 12 wk active voucher phase, 24 wk treatment phase Outpatient	**(1) CM alone** **(2) CM + CRA** All participants received a suicide risk assessment at each urine sample collection, but other formal treatment was not provided.	N=100 (41% female) outpatient treatment-seeking adults with CoUD	**Treatment retention:** Percent of participants still in treatment • CM+CRA > CM (84% vs 51%) at 12 weeks, the active voucher phase • CM+CRA > CM (65% vs 33%) at 24 weeks, the recommended amount of treatment **Stimulant abstinence**: Percent of stimulant-negative urine samples collected • CM+CRA > CM (78% vs 51%) at 12 weeks, the active CM phase. • No difference at 24 weeks, the recommended amount of treatment	

				Depressive symptoms (Not co-occurring MDD): Beck Depression Inventory II score for prior 30 days • CM+CRA > CM at 12 weeks, the active voucher phase (F(1,126)=8.1, p=0.005) • No difference between CM+CRA and CM at 24 weeks, the recommended amount of treatment **Psychiatric symptom severity**: Psychiatric problem composite core from the Addiction Severity Index No difference between CM+CRA and CM at 12 or 24 weeks	
Sanchez Hervas 2008[4] Sanchez Hervas 2010[5] Secades-Villa 2011[6] (Supplemental)	RCT, unblinded 24 weeks 12 mo follow-up Spain Outpatient	(1) **CRA** (n=47) (2) **TAU**: No protocol used; "techniques were applied in accordance with the therapist's clinical experience." However, "we used a cognitive–behavioural type intervention procedure" (n=35) 2 UDTs/week	N=82 adults with CoUD (DSM-IV-TR) within the Spanish public health system. Excluded severe psychopathological conditions (eg dementia, schizophrenia), those who presented a principal diagnosis for another psychoactive substance	**Continuous cocaine abstinence (self-report):** No sig difference between groups in % participants self-reporting continuous cocaine abstinence @ 12 months (27% vs 21%, n = 82, X^2 = 5.83, df=1, P = 0.65) **Cocaine abstinence rate (UDT):** Higher rate of abstinence in CRA group in completers-only analysis @ 12 months (95.2% vs 69.2%, n=34, X^2 =4.33, df=1, p=0.03, φ=0.35 [phi, medium effect]). ITT analysis assuming missing data not abstinent, no sig difference between groups @ 12 months (42.6% vs 25.7%, n=82, X^2 =4.64, df=1, p=0.09). **Treatment retention:** No sig difference in retention rate @ 6 months (26/47 [55%] vs 14/35 [40%], n=82, X^2 =1884, df=1, p=0.17). No sig difference in follow-up rate @ 12 months (21/47 [44%] vs 13/25 [37%], n=82, X^2 =0.576, df=1, p=0.44) **Addiction Severity (EuropASI):** Lower score @ 12 months in CRA group for Alcohol composite (0.07 vs 0.13, Mann-Whitney U=132.5, p=0.05) and Family/social composite (0.08 vs 0.21, U=110.5, p=0.012). However, higher baseline rate of history of alcohol abuse in TAU group vs CRA. EuropASI=European Addiction Severity Index	In systematic review: De Giorgi 2018[1]

Resources

Source	Resource	Comments
CRA+CM	NIDA, Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition), Community Reinforcement Approach Plus Vouchers (Alcohol, Cocaine, Opioids) (https://www.drugabuse.gov/publications/ principles-drug-addiction-treatment-researchbased-guide-third-edition/evidence-basedapproaches-to-drug-addiction-treatment/ behavioral-	

	therapies/community-reinforcementapproach-vouchers): This resource describes the Community Reinforcement Approach (CRA) Plus Vouchers, an intensive 24-week outpatient therapy that combines counseling, vocational services, recreational and social activities, and material incentives to help patients maintain abstinence.	

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CRA vs TAU: Network meta-analysis with no direct comparisons Found 1 RCT of CRA vs TAU for CoUD (n=82), where CRA group had a small 6% more participants of 24 weeks CRA vs CM: None CRA vs CBT: **CRA vs Other:** CRA appears to achieve somewhat better results sometimes at end of treatment and typically in longer term follow up for outcomes of abstinence duration, abstinence rates, and treatment retention compared to all other treatments among individuals with cocaine use disorder. **CRA+CM vs CRA: Moderate** CM + CRA generally superior to CRA alone on stimulant abstinence and time to use after period of abstinence, and treatment completion. No difference found on time in treatment. Mixed results on psychosocial functioning.	**CRA vs Other:** It does not appear that CRA has been tested for methamphetamine use disorders. **CRA+CM vs CRA: Moderate, None** All evidence based on participants with cocaine use disorder. While there is no contraindication for CRA+CM for MaUD, there is no research evidence to support it. The CGC expects it would be clinically effective for MaUD This judgment is primarily based on the evidence, as no members of the CGC have direct experience with CRA.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CRA vs TAU: **CRA vs CM: None** no undesirable effects **CRA vs CBT:** **CRA vs Other: None**		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

There are no obvious undesirable effects of CRA. **CRA+CM vs CRA: None** no undesirable effects reported		
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
CRA vs TAU: **CRA vs CM:** Favors intervention **CRA vs CBT:** **CRA vs Other: substantially favors intervention** Since there are apparent benefits to CRA, at least for cocaine use disorder, and no obvious undesirable effects, the balance substantially favors the intervention. **CRA+CM vs CRA: Substantially favors intervention** The balance of effects favors CM+CRA vs CRA alone.	**CRA vs CM:** None **CRA+CM vs CRA: Substantially favors** Substantially favors adding CM to CRA. Based on the available evidence	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
CRA vs TAU: **CRA vs CM:** Same as above. **CRA vs CBT:** **CRA vs Other:** For cocaine use disorder the certainty of the evidence is modest given that CRA did not outperform other treatments on all occasions when outcomes were measured. The quality of the evidence favoring CRA seems to be high given that it comes from well conducted, randomized, clinical trials. **CRA+CM vs CRA: Moderate**	**CRA vs CM:** None **CRA vs Other:** Certainty and quality here do not align perfectly. **CRA+CM vs CRA: Moderate** While evidence is only in for CoUD, expect it to also be effective for treatment of ATSUD, but this should be studied directly. Based on long-term outcomes, not during trial period. Reduce overall certainty given inclusion of an unstudied population.	☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High

Quality of evidence is adequate to assert that CM+CRA is superior to CRA alone. Moderate for the field given study sample sizes.		
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence found in systematic review.	CRA vs Other: People seeking treatment for stimulant use disorder obviously must value abstinence, or otherwise they would not seek treatment. People seeking treatment probably care less about how long they remain in treatment; they just want to get better. Since CRA typically tries to include family members, individuals without current family contact might not be good candidates for this modality. CRA+CM vs CRA: No No expected uncertainty in value for main outcomes that were examined.	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
* **Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence found in systematic review.	CRA vs Other: Any treatment like CRA that is more costly and requires more resources will be less accessible to individuals without insurance, or who are otherwise economically disadvantaged and may increase inequity. However, if treatment is effective, it should benefit those more adversely affected, and so reduce disparities. CRA+CM vs CRA: Probably reduced Reduced based on benefit of treatment differentially affecting those most impacted. Due to lack of direct evidence, will say probably. Also, research priority should be evaluating cultural appropriateness for specific minority populations. If implemented broadly or in underserved populations, has the potential to reduce health inequity.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
* **Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*

Since CRA has not been widely used in routine clinical care the question of acceptability remains unanswered.	CRA vs TAU: CRA vs CM: CRA vs CBT: CRA vs Other: CRA does require more time commitment on the part of the patient. Some patients may not be interested or willing to make that commitment. Since CRA has not been widely implemented outside of research settings, it is not clear how acceptable it would be to most real-world patients. It is also not clear how readily payors would support it. CRA+CM vs CRA: Probably yes	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
CRA vs TAU: CRA vs CBT: CRA vs Other: No direct evidence found in systematic review. CRA+CM vs CRA: Probably yes No direct evidence found in systematic review.	CRA itself is resource intensive and few settings have the workforce appropriately trained to implement it. CRA vs Other: It would have to be studied for methamphetamine use disorder before it is applied widely to treat people with that disorder. At the present time it does not appear feasible to implement CRA widely. It would be necessary to train the workforce and assure it can be paid for. CRA requires more resources than CBT or TAU. Only an economic analysis could inform us as to whether it is really cost-effective compared to other treatments. Unknown if it could be widely implemented given extensive program resource requirements. CRA vs CM: Same as above CRA+CM vs CRA: Probably yes CM+CRA requires more resources and patient time than does CRA alone. An economic analysis could determine if the increase in resources is worth the investment in terms of QALYs.	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Randomized trials indicate that CRA is slightly superior to treatment as usual and to CBT at long term follow up. While there is less direct evidence, the combination of CRA and CM is superior to CM only across a range of outcomes. While evidence supports the use of CRA, the committee recognizes significant implementation barriers, resource requirements, and lack of training.

Subgroup Considerations

None known.

Implementation Considerations

- There are substantial barriers to implementation of CRA. Very few, if any, experts are available to train clinicians in delivery of CRA. CRA is also costly and labor intensive so funding and staff levels would have to be increased to implement it adequately.
- Clinicians should consider a patient's age, sex, gender identity, race, ethnicity, sexual orientation, and other sociocultural factors that may impact their stimulant use when choosing or designing a treatment or recovery plan. Refer to the Health Disparities section for additional guidance.

Research Priorities

- Direct evidence of effectiveness of CRA for amphetamine-type stimulant use disorder.
- Evaluating cultural appropriateness of CRA for specific minority populations.
- Implementation barriers for CRA.

References

1. De Giorgi R, Cassar C, Loreto D'alò G, et al. Psychosocial interventions in stimulant use disorders: a systematic review and qualitative synthesis of randomized controlled trials. *Riv Psichiatr*. 2018;53(5):233-255. doi:10.1708/3000.30003
2. De Crescenzo F, Ciabattini M, D'Alò GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. Degenhardt L, ed. *PLoS Med*. 2018;15(12):e1002715. doi:10.1371/journal.pmed.1002715
3. Higgins ST, Sigmon SC, Wong CJ, et al. Community Reinforcement Therapy for Cocaine-Dependent Outpatients. *Arch Gen Psychiatry*. 2003;60(10):1043-1052. doi:10.1001/archpsyc.60.9.1043
4. Sánchez Hervás E, Zacarés Romaguera FD, García Rodríguez O, Secades Villa R, Fernández Hermida JR. Community reinforcement approach (CRA) for cocaine addicts: Establishment in a public health setting. *Anales de Psiquiatria*. 2008;24(4):153–158.
5. Sánchez Hervás E, Secades Villa R., Zacarés Romaguera FD, García Fernández G, Santonja Gómez FJ, García Rodríguez O. Behavioral therapy for cocaine addicts: Outcomes of a follow-up six month study. *Revista Mexicana de Psicología*. 2010;27(2):159-167. https://digibuo.uniovi.es/dspace/handle/10651/10653
6. Secades-Villa R, Sánchez-Hervás E, Zacarés-Romaguera F, García-Rodríguez O, Santonja-Gómez FJ, García-Fernández G. Community Reinforcement Approach (CRA) for cocaine dependence in the Spanish public health system: 1 year outcome: CRA for cocaine dependence. *Drug Alcohol Rev*. 2011;30(6):606-612. doi:10.1111/j.1465-3362.2010.00250.x

Table 3. Cognitive Behavioral Therapy

Recommendation: The following three interventions have the most supportive evidence and are preferred alongside contingency management: CRA, **Cognitive Behavioral Therapy (CBT),** and the Matrix Model.

Clinical Question Summary Table

Clinical Question	1. Is CBT (with or without background treatment) effective at reducing stimulant use and increasing treatment retention in patients in treatment for stimulant use disorder? 2. Is CBT more effective than other behavioral treatments for stimulant use disorder? 3. Does adding Contingency Management to CBT improve outcomes for StUD? 4. What additional considerations and implementation strategies may influence the effects of CBT?
Population	Patients with stimulant use disorder
Intervention	Cognitive Behavioral Therapy (CBT)
Comparison	Treatment as usual or Other behavioral treatment (excluding CM and CRA, addressed in their respective tables)
Main Outcomes	Stimulant abstinence, stimulant use, treatment retention
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Cognitive Behavioral Therapy (CBT) is a treatment that focuses on... CBT-RP: Marlatt's model of CBT relapse prevention CBT-BAT: Behavioral Activation Therapy goal-oriented evidence-based CBT for depression and HIV risk-reduction counseling (Mimiaga 2012; 2012; 2018/2019) Matrix model CBT G-CBT
Abbreviations	**ACT:** Acceptance and commitment therapy, **ATS**: Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CBT**: Cognitive Behavioral Therapy, **CM**: Contingency Management, **CoUD**: Cocaine use disorder, **DAM**: diacetylmorphine maintenance for heroin dependence, **GSST**: Gay social support therapy, **IOP:** Inpatient/Outpatient, **IPT**: Interpersonal Therapy, **MA**: Methamphetamine, **MaUD**: Methamphetamine Use Disorder, **Mgmt**: Management, **MMT**: Methadone Maintenance Therapy **MPH**: Methylphenidate, **MSM**: Men who have sex with men, **N**: Number, **n.r.**= Not Reported, **NSD**: No significant difference, **RCT:** Randomized control trial, **RoB**: Risk of Bias, **SEPT**: , **SMD:** Standard mean difference, **StUD**: Stimulant use disorder, **TAU:** Treatment as usual, **TSF:** Twelve step facilitation
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Meta-analysis Tran et al (2021) not included; CBT interventions were Brief CBT.

CBT vs TAU/Control

Summary of Findings Table: CBT vs TAU/Control:

Outcome	Importance	Strength of Evidence[i]	Effect/ Source (Quality[ii])	Studies	Comments
Continuous stimulant abstinence @ 12 weeks	Critical	Moderate	**No effect** 1 network meta-analysis • De Crescenzo 2018[1] (High) 21 RCTs 1 meta-analysis • De Crescenzo 2018[1] (High) 2 RCTs, n=211; I-squared=46.4%, p=0.172	2 trials, 211 participants • Carroll 1994b (reanalysis of Carroll 1994a, n=110 CoUD, 12 wks CBT RP + Desipramine/Placebo vs Clinical Mgmt + Desipramine/Placebo); Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT)	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
Continuous stimulant abstinence @ trial end	Critical	Moderate	**No effect** 1 network meta-analysis • De Crescenzo 2018[1] (High) 25 RCTS 1 meta-analysis • De Crescenzo 2018[1] (High) 2 RCTs, n=211; I-squared=46.4%, p=0.172 **Positive effect for CBT** 1 systematic review • AshaRani 2020[2] (Moderate-High) 1 RCT, n=41	3 trials, 252 participants • Carroll 1994b (reanalysis of Carroll 1994a, n=110 CoUD, 12 wks CBT RP + Desipramine/Placebo vs Clinical Mgmt + Desipramine/Placebo); Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT); Mimiaga 2018 (n=41 MaUD MSM, CBT-BAT vs Health education)	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
Stimulant abstinence @ 12 weeks	Critical	Moderate	**No effect** 1 network meta-analysis • De Crescenzo 2018[1] (High) 42 RCTs 1 meta-analysis • De Crescenzo 2018[1] (High) 6 RCTs, n=691; I-squared=69%, p=0.006	6 trials, 691 participants • Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT); Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling + TAU vs TAU=Group counseling); Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in MMT, CBT+MPH/Placebo vs TAU+MPH/Placebo); McKay 1997 (n=98	Cocaine/ MA abstinence rate (% UDS-)

				CoUD men, 24 wk CBT-RP vs Group counseling); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT); Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST)	
Stimulant abstinence @ trial end	Critical	Low	**No effect** 1 network meta-analysis • De Crescenzo 2018[1] (High) 46 RCTs 2 meta-analyses: • De Crescenzo 2018[1] (High) 6 RCTs, n=691; I-squared=71.1%, p=0.004 • Harada 2018[3] (Moderate) 1 RCTs, n=210, SMD= -0.28, 95% CI -0.69 to 0.14, p=0.19 **Positive effect for CBT** 1 systematic review • De Giorgi 2018[4] (Moderate) Positive effects in 5 of 7 studies found	11 trials, 1240 participants • Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT); Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling + TAU vs TAU=Group counseling); Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in MMT, CBT+MPH/Placebo vs TAU+MPH/Placebo); McKay 1997 (n=98 CoUD men, 24 wk CBT-RP vs Group counseling); Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT); Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST); Martin 2010 (n=50 MDMA use, 1-session Brief CBT vs Wait-list) RoB Low; Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP + Disulfiram vs TSF + Disulfiram vs TAU + Disulfiram, TAU=Clinical Mgmt); Carroll 2004 (n=121 CoUD, 12 wk CBT + Disulfiram/Placebo vs TAU + Disulfiram/Placebo, TAU=IPT); Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TAU, TAU=TSF); Monti 1997 (n=128 CoUD/use, 1-3 wk Brief CBT vs TAU, TAU=Attention control)	Cocaine/ MA abstinence rate (% UDS-)
Stimulant abstinence @ furthest follow up	Critical	Low	**No effect** 1 network meta-analysis • De Crescenzo 2018[1] (High) 32 RCTs	3 trials, 430 participants • Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling) Unclear RoB; Rawson 2002 (n=108 CoUD &	Cocaine/ MA abstinence rate (% UDS-)

			1 meta-analysis: • De Crescenzo 2018[1] (High) 3 RCTs, n=430; I-squared=72%, p=0.028	OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) Unclear RoB; Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) Unclear RoB	
Treatment retention @12 wks	Critical	Low	**Positive effect for CBT** 1 network meta-analysis • De Crescenzo 2018[1] (High) OR (95% CI) = 1.42 (1.05, 1.93), p=n.r., 41 RCTs 1 meta-analysis • De Crescenzo 2018[1] (High) 5 RCTs, n=643, OR (95% CI) = 0.69 (0.5, 0.94), p=n.r.; I-squared=0%	5 trials, 643 participants • Carroll 1994b (Carroll 1994a reanalysis, n=110 CoUD12 wks, CBT RP + Desipramine/Placebo vs Clinical Mgmt + Desipramine/Placebo; Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT); Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling + TAU vs TAU=Group counseling/TSF); Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in DAM maintenance, 12 wk CBT+MPH/Placebo vs TAU+MPH/Placebo, TAU= DAM maintenance); Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST)	Dropout rate (%n):
Treatment retention @ trial end	Critical	Low	**Positive effect for CBT** 1 network meta-analysis • De Crescenzo 2018[1] (High) OR (95% CI) = 1.47 (1.08, 2), p=0.014. 43 RCTS 1 meta-analysis • De Crescenzo 2018[1] (High) 5 RCTs, n=643, OR (95% CI) = 0.66 (0.47, 0.92), p=n.r., I-squared=0%	5 trials, 643 participants • Carroll 1994b (Carroll 1994a reanalysis, n=110 CoUD12 wks, CBT RP + Desipramine/Placebo vs Clinical Mgmt + Desipramine/Placebo); Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT); Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling + TAU vs TAU=Group counseling/TSF); Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in DAM maintenance, 12 wk CBT+MPH/Placebo vs TAU+MPH/Placebo, TAU= DAM maintenance); Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST)	Dropout rate (%n):

Return to stimulant use after a period of abstinence	Important	Very low	**Positive effect for CBT Relapse Prevention** 1 systematic review • AshaRani 2020[2] (Moderate-High) 1 quasi-experimental, n=41, CBT v TAU relapse rate 49.4% vs 70.7%)	1 trial, 80 participants • Abdoli 2019 (Quasi-experimental n=80 MaUD women Iran, Marlatt CBT Relapse Prevention vs TAU) All female sample. Relapse rate measure was not described, probably self-report.	
Drug use	Important	Low	**Positive effect for CBT** 1 Meta-analysis: • Harada 2018[3] (Moderate) 2 RCTs, n=210, OR -0.28, 95% CI -0.69 to 0.14, p=0.19); I-squared=28%, p=0.24.	2 trials, 210 participants • Martin 2010 (n=50 MDMA use, 1-session Brief CBT vs Wait-list); Tait 2015 (n=160 non-treatment seeking MaUD, web-based CBT vs Wait-list) RoB High	

[i]: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Detailed Findings: CBT vs TAU/Control

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ 12 weeks	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** between CBT and TAU in a network meta-analysis of 21 RCTS. **No difference** between CBT and TAU in pairwise meta-analysis: 2 RCTs, 211 participants; I-squared=46.4%, p=0.172: • Carroll 1994b (reanalysis of Carroll 1994a, n=110 CoUD, 12 wks CBT RP+Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo) **High RoB;** Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation)**	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
Continuous stimulant abstinence @ trial end	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** between CBT and TAU in a network meta-analysis of 25 RCTS. **No difference** between CBT and TAU in pairwise meta-analysis: 2 RCTs, 211 participants; I-squared=46.4%, p=0.172: • Carroll 1994b (reanalysis of Carroll 1994a, n=110 CoUD, 12 wks CBT RP + Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo) **High RoB;** Carroll	Longest duration (in weeks) of cocaine/MA abstinence (UDS)

			2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation)**	
		Systematic review: AshaRani 2020[2] (Moderate-High)	**Positive for CBT Behavioral Activation** compared to TAU in days of MA abstinence (51.1 vs 39 days) in 1 study of MSM: • Mimiaga 2018 (n=41 MaUD MSM, CBT-BAT vs Health education) Some concerns	MSM sample
Stimulant abstinence @ 12 weeks	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** between CBT and TAU in a network meta-analysis of 42 RCTS.	Cocaine/ MA abstinence rate (% UDS-)
			No difference between CBT and TAU in pairwise meta-analysis: 6 RCTs, 691 participants; I-squared=69%, p=0.006: • Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation);** Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling) **Unclear RoB (reporting);** Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in MMT, CBT+MPH/Placebo vs TAU+MPH/Placebo) **Unclear RoB (random, allocation);** McKay 1997 (n=98 CoUD men, 24 wk CBT-RP vs Group counseling) **Unclear RoB (allocation, blinding, attrition);** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) **Unclear RoB (randomization, allocation)**	
Stimulant abstinence @ trial end	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** between CBT and TAU in a network meta-analysis of 46 RCTS. **No difference** between CBT and TAU in pairwise meta-analysis: 6 RCTs, 691 participants; I-squared=71.1%, p=0.004: • Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation);** Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling) **Unclear RoB (reporting);** Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in MMT, CBT+MPH/Placebo vs TAU+MPH/Placebo) **Unclear RoB (random, allocation);** McKay 1997 (n=98 CoUD men, 24 wk CBT-RP vs Group counseling) **Unclear RoB (allocation, blinding, attrition);** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting)**; Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) **Unclear RoB (randomization, allocation)** Author evaluation of the quality of the mixed evidence	Cocaine/ MA abstinence rate (% UDS-)

			• Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Meta-analysis: Harada 2018[3] (Moderate)	**No difference** between CBT and Wait-list Control in stimulant abstinence rate (%) at 90 days: 1 study, n=-50, OR 0.22, 95% CI 0.02 to 2.11, p=0.19. • Martin 2010 (n=50 MDMA use, 1-session Brief CBT vs Wait-list) RoB Low	
		Systematic review: De Giorgi 2018[4] (Moderate)	**Positive for CBT** compared to TAU in five out of seven studies: • Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt); Carroll 2004 (n=121 CoUD, 12 wk CBT+Disulfiram/Placebo vs TAU+Disulfiram/Placebo, TAU=IPT); Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TAU, TAU=TSF); Monti 1997 (n=128 CoUD/use, 1-3 wk Brief CBT vs TAU, TAU=Attention control)	TAU: 12-step facilitation, group therapy, individual therapy)
			Positive for CBT Relapse Prevention compared to TAU for patients with cocaine use disorders: • Carroll 1991 (n=42 CoUD/use, 12 wk CBT-RP vs IPT); Carroll 1994a (n=110 CoUD12 wks, CBT RP+Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo); Carroll 1994b (Carroll 1994a reanalysis, n=110 CoUD12 wks, CBT RP+Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo); Wells 1994 (n=110 CoUD/use, 12 wk CBT-RP vs TSF) **Positive for CBT Relapse Prevention** compared to TAU only for participants who were cocaine abstinent during the active treatment phase of IOP: • McKay 1997 (n=98 CoUD men, 24 wk CBT-RP vs Group counseling) **Positive for CBT** compared to TAU for twice-weekly and biweekly CBT: • Covi 2002 (n=68 CoUD & Other SUD, 12 wks CBT every 2 wks vs CBT 1/wk vs CBT 2/wk) **Positive for CBT Relapse Prevention** compared to TAU for group and individual CBT RP: • Schmitz 1997 (n=32 CoUD, 8 wk group CBT-RP vs individual CBT-RP)	

Stimulant abstinence @ furthest follow up	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** between CBT and TAU in a network meta-analysis of 32 RCTs. **No difference** between CBT and TAU in pairwise meta-analysis: 3 RCTs 3, n=430; I-squared=72%, p=0.028: • Crits-Christoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling) **Unclear RoB (reporting);** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) **Unclear RoB (randomization, allocation)**	Cocaine/ MA abstinence rate (% UDS-)
Treatment retention @12 wks	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CBT** compared to TAU: OR (95% CI) = 1.42 (1.05, 1.93), p=n.r. in a network meta-analysis of 41 RCTS. **Positive for CBT** compared to TAU: 5 RCTs, 643 participants, OR (95% CI) = 0.69 (0.5, 0.94), p=n.r.; I-squared=0%: • Carroll 1994b (Carroll 1994a reanalysis, n=110 CoUD12 wks, CBT RP+Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo) **High RoB;** Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling/TSF) **Unclear RoB (reporting)**; Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in DAM maintenance, 12 wk CBT+MPH/Placebo vs TAU+MPH/Placebo, TAU= DAM maintenance) **Unclear RoB (random, allocation);** Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) **Unclear RoB (randomization, allocation)**	12-week dropout rate (%n):

Treatment retention @ trial end	N/A	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CBT** compared to TAU @ trial end: OR (95% CI) = 1.47 (1.08, 2), p=0.014. Based on a network meta-analysis of 43 RCTS. **Positive for CBT** compared to TAU @ trial end: 5 RCTs, 643 participants, OR (95% CI) = 0.66 (0.47, 0.92), p=n.r.; I-squared=0%. • Carroll 1994b (Carroll 1994a reanalysis, n=110 CoUD12 wks, CBT RP+Desipramine/Placebo vs Clinical Mgmt+Desipramine/Placebo) **High RoB;** Carroll 2014 (n=101 CoUD & OUD, 8 wks CBT4CBT+MMT vs MMT) **Unclear RoB (allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group counseling/TSF) **Unclear RoB (reporting);** Dürsteler-MacFarland 2013 (n=62 CoUD & OUD in DAM maintenance, 12 wk CBT+MPH/Placebo vs TAU+MPH/Placebo, TAU= DAM maintenance) **Unclear RoB (random, allocation);** Shoptaw 2008 (n=96 StUD MSM, 16 wk G-CBT vs GSST) **Unclear RoB (randomization, allocation)** Author evaluation of the quality of the mixed evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	12-week dropout rate (%n):
Outcome Importance: Important				
Stimulant relapse rate	N/A	Systematic review: AshaRani 2020[2] (Moderate-High)	**Positive for CBT Relapse Prevention** compared to TAU in rate of return to stimulant use after a period of abstinence (49.4 vs 70.7). Measure of relapse was not described, probably self-report. • Abdoli 2019 (Quasi-experimental n=80 MaUD women Iran, Marlatt CBT Relapse Prevention vs TAU) **High RoB**	All female sample
Drug use	N/A	Meta-analysis: Harada 2018[3] (Moderate)	**No difference** between CBT and Wait-list Control in stimulant abstinence rate (%) at 90 days (2 studies, n=210, OR -0.28, 95% CI -0.69 to 0.14, p=0.19); I-squared=28%, p=0.24. • Martin 2010 (n=50 MDMA use, 1-session Brief CBT vs Wait-list) **Low RoB;** Tait 2015 (n=160 non-treatment seeking MaUD, web-based CBT vs Wait-list) **High RoB** **Author assessment of evidence quality (GRADE): Low.** Quality downgraded two levels because of limitations in the design and implementation of included studies (blinding and attrition) and imprecision of results (small sample size).	ATStUD

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CBT vs CM

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ 12 wks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CM** compared to CBT: SMD (95% CI) = -0.56 (-0.88, -0.23), p=n.r. Network meta-analysis of 21 RCTS	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
			Positive for CM compared to CBT: 2 RCTs, 217 participants, SMD (95% CI) = -0.65 (-0.96, -0.034), p=n.r. I-squared=19.8%, p=0.264. Pairwise meta-analysis: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**. CM alone > CBT Matrix Model alone: 5.1 vs 2.1 weeks	
Continuous stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CM** compared to CBT: SMD (95% CI) = -0.5 (-0.78, -0.23), p=n.r. Network meta-analysis of 25 RCTS	Longest duration (in weeks) of cocaine/MA abstinence (UDS)
			Positive for CM compared to CBT: 2 RCTs, 217 participants, SMD (95% CI) = -0.65 (-0.96, -0.34), p=n.r.; I-squared=19.8%, p=0.264: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	
		RCT: Rawson 2006[5] (Supplemental)	**Positive for CM alone** compared to Matrix Model alone: higher percentage of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial compared to CBT Matrix Model alone (60% vs 34.5%). (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model)	Unclear RoB
Stimulant abstinence @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 42 RCTs • **Positive for CM** compared to CBT: OR (95% CI) = 0.51 (0.33, 0.79), p=n.r. Pairwise meta-analysis • **Positive for CM** compared to CBT: 4 RCTs, 395 participants, OR (95% CI) = 0.43 (0.27, 0.68), p=n.r.; I-squared=0%: Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB** No sig diff bn groups; Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs	

			CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization)** No sig diff bn groups; Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)** CM > CBT 5.1 vs 2.1 weeks	
Stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 46 RCTs • **Positive for CM** compared to CBT: OR (95% CI) = 0.53 (0.35, 0.81), p=0.003. Pairwise meta-analysis • **Positive for CM** compared to CBT: 4 RCTs, 395 participants, OR (95% CI) = 0.43 (0.27, 0.68), p=n.r.; I-squared=0%: Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Low; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Meta-analysis: Minozzi 2016[6] (Supplemental)	**No difference** in abstinence rate (%n) @ end of treatment (1 RCT, n=55, RR 0.66 [0.38,1.16], p=0.15)	Cochrane Review
		Systematic review: AshaRani 2020[2] (Moderate-High)	**CM** showed the strongest evidence in promoting abstinence and reducing methamphetamine use, although CBT was also effective. “CM, CBT and exercise demonstrated clear efficacy in reducing METH use and thus should continue to be the first line of treatment for METH dependence in the absence of effective pharmacotherapy” (p. 17).	
		Systematic review: Farronato 2013[7] (Supplemental)	**Positive for CM** compared to CBT: CM resulted in reduced cocaine use during active treatment in all eight included RCTs (n=1093). CBT demonstrated less reliable benefit with no positive effect during active treatment, but showed delayed positive results in three out of five trials.	

			• Kirby 1998 (n=90 CoUD, CM + Individual CBT vs Individual CBT); McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Rowan-Szal 2005 (n=61 cocaine use OUD in MMT); Schnitz 2008 (n=161 CoUD, 12 wks CM + CBT + Clinical management + Placebo vs CM + CBT + Clinical management + levodopa/carbidopa 400/100 mg bid vs CBT + Clinical management + Placebo vs CBT + Clinical management + levodopa/carbidopa 400/100 mg bid); Schmitz 2009 (n=87 CoUD & AUD, 12 wks CM + CBT + Placebo vs CM + CBT + Naltrexone 100 mg/d vs CBT + Placebo vs CBT + Naltrexone 100 mg/d)	
Stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 32 RCTs • **No difference** Pairwise meta-analysis • **No difference**. 4 RCTs, 395 participants; I-squared=0%: Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	
		Meta-analysis: Minozzi 2016[6] (Supplemental)	**No difference** in abstinence rate (%n) (1 RCT, n=55, RR 1.17 [0.73, 1.87], p=0.51)	Cochrane Review
		Systematic review: Farronato 2013[7] (Supplemental)	**CBT = CM**: "In 3 of the 5 studies with follow-up appointments, a positive effect of **CBT** emerged post-treatment... so-called sleeper effects." 5 RCTs, n=732: • McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); Rowan-Szal 2005 (n=61 cocaine use OUD in MMT)	
Treatment retention @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** Network meta-analysis of 41 RCTs **No difference**. Pairwise meta-analysis of 2 RCTs, 213 participants; I-squared=0%: • Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Rawson 2006 (n=177 CoUD/MaUD, CM	Dropout rate (%n)

			alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization)** CM > CBT 63% vs 40%	
Treatment retention @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis 43 RCTs • **No difference**: OR (95% CI) = 1.04 (0.73, 1.48), p=0.838 Pairwise meta-analysis • **No difference**. 2 RCTs, 213 participants; I-squared=0%. Epstein 2003 (n=286 CoUD & OUD in MMT, CBT+CM+TAU vs CBT+NCR+TAU vs CM+TAU vs NCR+TAU) **High RoB;** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization)** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)
Duration of treatment	Low	RCT: Rawson 2006[5] (Supplemental)	**Positive for CM alone** compared to CBT Matrix Model alone: CM alone had more average weeks retained in treatment compared to CBT Matrix Model alone (12.6 vs 9 weeks) (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model vs CM+CBT Matrix Model)	
		RCT: Shoptaw 2005[8] (Supplemental)	**Positive for CM alone** compared to CBT Matrix Model alone: CM alone had more average weeks retained in treatment compared to CBT Matrix Model alone (12 vs 8.9 weeks) (n=162 OPT-seeking MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT)	
Outcome Importance: Important				
Stimulant craving	Low	Systematic review: AshaRani 2020[2] (Moderate-High)	**CM** showed the strongest evidence in reducing methamphetamine craving, although **CBT** was also effective.	
Sexual risk-taking behavior	Low	RCT: Shoptaw 2005[8] (Supplemental)	• **Positive for G-CBT** compared to CM alone, CBT Matrix Model alone, CM+CBT: G-CBT (tailored gay and bisexual men-specific Matrix Model CBT) showed greater initial reductions in unprotected receptive anal intercourse in the first 4 weeks of treatment relative to other conditions ($\chi 2$ (3) = 6.75, $p < .01$). This difference did not persist at 6- or 12-month follow-up. • **No difference** between CM alone, Matrix Model CBT alone, and CM+CBT; equivalent declines in self-reported sexual risk-taking behaviors such as incidence of unprotected anal intercourse and number of prior 30-day sexual partners	

			• n=162 tx-seeking MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT	

CBT vs CRA

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 25 RCTs. No studies for pairwise analysis.	Longest duration of cocaine/MA abstinence (weeks)
Continuous stimulant abstinence during follow-up	Moderate	Systematic review: De Giorgi 2018[4] (Moderate)	**No difference** in self-reported cocaine/MA abstinence during the follow-up period 1 no effect (2 publications on same data-set): (1 RCT, n=82) • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) Self-report cocaine use	
Stimulant abstinence @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 42 RCTs. No studies for pairwise analysis.	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 46 RCTs. **No difference** in pairwise meta-analysis: 1 RCT, 74 participants: • Sanchez-Hervas 2010 (n=82 CoUD in Spain, 24 wks CRA vs TAU) **High RoB** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CRA** compared to CBT in network meta-analysis of 32 RCTs: OR (95% CI) = 0.39 (0.17, 0.91), p=n.r. **Positive for CRA** compared to CBT in pair-wise meta-analysis: 1 RCT, 74 participants, OR (95% CI) = 2.77 (1.04, 7.41), p=n.r.: • Sanchez-Hervas 2010 (n=82 CoUD in Spain, 24 wks CRA vs TAU) **High RoB**	Cocaine/MA abstinence rate (% UDS-)

		Systematic review: De Giorgi 2018[4] (Moderate)	**Positive for CRA:** CRA > TAU cocaine abstinence rate (%n UDS-) 1 mixed effect (2 publications on same data-set): (1 RCT) • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) CRA>TAU in completers-only analysis (95% vs 69%). NSD @ 12 months in ITT analysis assuming missing-positive	
Treatment retention@ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 41 RCTs. No studies for pairwise analysis.	Dropout rate (%n)
Treatment retention@ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 43 RCTs. **No difference** in pairwise meta-analysis: 1 RCT, 74 participants: • Sanchez-Hervas 2010 (n=82 CoUD in Spain, 24 wks CRA vs TAU) **High RoB** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Very low; Study limitations: major concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)
		Systematic review: De Giorgi 2018[4] (Moderate)	**Positive for CRA:** CRA had higher retention rate (%n) (55% vs 40%) 1 no effect (2 publications on same data-set): (1 RCT) • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, CRA vs TAU [CBT w/out protocol]) NSD @ 24 wks	
Outcome Importance: Importance				
Psychosocial functioning @ 12 months	N/A	Systematic review: De Giorgi 2018[4] (Moderate)	**Positive for CRA:** CRA had greater improvements in ASI composite scores 1 positive effect (2 publications on same data-set): (1 RCT) • Sanchez Hervas 2008; Secades-Villa 2011 (n=82 CoUD Spain, 24 wks CRA vs TAU [CBT w/out protocol]) CRA>TAU in Alcohol and Family/social composite	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CBT+CM vs CRA+CM

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				

Continuous stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 25 RCTs. No studies for pairwise analysis.	Longest duration of cocaine/MA abstinence (weeks)
Stimulant abstinence @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 42 RCTs: OR (95% CI) = 0.4 (0.17, 0.92), p=n.r. No studies for pairwise analysis.	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 46 RCTs. No studies for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Cocaine/MA abstinence rate (% UDS-)
Stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 32 RCTs: OR (95% CI) = 0.4 (0.17, 0.98), p=n.r. No studies for pairwise analysis.	Cocaine/MA abstinence rate (% UDS-)
Treatment retention@ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in network meta-analysis of 41 RCTs. No studies for pairwise analysis.	Dropout rate (%n)
Treatment retention@ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**Positive for CRA:** Higher in CRA+CM compared to CBT+CM in network meta-analysis of 43 RCTs: OR (95% CI) = 0.39 (0.19, 0.79), p=0.009. No studies for pairwise analysis. Author evaluation of the quality of indirect evidence • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: no concerns; Heterogeneity: some concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (%n)

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CM+CBT vs CBT

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				

Continuous stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 21 RCTs • **Positive for CM+CBT** compared to CBT: SMD (95% CI) = -0.69 (-1.12, -0.26), p=n.r. Pairwise meta-analysis • **Positive for CM+CBT** compared to CBT: 2 RCTs, 217 participants, SMD (95% CI) = 0.71 (0.29, 1.12), p=n.r.; I-squared=54.2%, p=0.14 Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
Continuous stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 25 RCTs • **Positive for CM+CBT** compared to CBT: SMD (95% CI) = -0.65 (-0.96, -0.34), p=n.r. Pairwise meta-analysis • **Positive for CM+CBT** compared to CBT: 2 RCTs, 277 participants, SMD (95% CI) = 0.63 (0.31, 0.94), p=n.r.; I-squared=38.6%, p=0.196 Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
		Systematic review: AshaRani 2020[2] (Moderate-High)	**Positive for GCBT compared to CM + GCBT** in consecutive weeks of MA abstinence (-0.44, CI: -0.79, -0.09) in 1 RCT: • Reback & Shoptaw 2014 (n=257 MaUD MSM, CM vs CBT vs CM+CBT vs G-CBT); Sanchez-Hervas 2010	
		Systematic review: Farronato 2013[7] (Supplemental)	**No difference** between CM+CBT and CM alone in weeks of continuous cocaine abstinence and number of cocaine-free urine samples in 1 RCT. Cocaine use stayed high throughout the study. • Kirby 1998 (n=90 CoUD, CM + Individual CBT vs Individual CBT)	
Stimulant abstinence rate @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 42 RCTs • **Positive for CM+CBT** compared to CBT: OR (95% CI) = 0.44 (0.27, 0.72), p=n.r. Pairwise meta-analysis • **Positive for CM+CBT** compared to CBT: 6 RCTs, 553 participants, OR (95% CI) = 2.32 (1.57, 3.41), p=n.r.; I-squared=1.4%, p=0.407:	Cocaine/MA abstinence rate (% UDS-)

			Carroll 2016 (n=100 CoUD, CBT+CM+Disulfiram vs CBT+CM+Placebo vs CBT+Disulfiram vs CBT+Placebo) **Unclear RoB (allocation);** Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Petitjean 2014 (n=60 CoUD, 6 mo CM+CBT vs CBT-only) **Low RoB;** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	
Stimulant abstinence rate @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 46 RCTs • **Positive for CM+CBT** compared to CBT: OR (95% CI) = 0.48 (0.3, 0.78), p=0.002. Confidence in estimate: Low Pairwise meta-analysis • **Positive for CM+CBT** compared to CBT: 6 RCTs, 553 participants, OR (95% CI) = 2 (1.22, 3.26), p=n.r.; I-squared=38.4%, p=0.15: Carroll 2016 (n=100 CoUD, CBT+CM+Disulfiram vs CBT+CM+Placebo vs CBT+Disulfiram vs CBT+Placebo) **Unclear RoB;** Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Petitjean 2014 (n=60 CoUD, 6 mo CM+CBT vs CBT-only) **Low RoB;** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB;** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB;** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Low; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: major concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Cocaine/MA abstinence rate (% UDS-)
		Systematic review: Farronato 2013[7] (Supplemental)	**Positive for CM+CBT** compared to CBT**:** 2 RCTs both found higher rates cocaine-free samples in CM+CBT vs CBT conditions.	

			• McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU); ~~Rawson 2006~~ (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model)	
Stimulant abstinence rate @ farthest follow-up	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 32 RCTs • **No difference** Pairwise meta-analysis o **No difference**: 5 RCTs, 454 participants; I-squared=42.5%, p=0.121 o Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB** ; Petitjean 2014 (n=60 CoUD, 6 mo CM+CBT vs CBT-only) **Low RoB;** Rawson 2002 (n=108 CoUD & OUD, 16 wk CM+CBT+MMT vs CM+MMT vs CBT+MMT vs MMT) **Unclear RoB (randomization, allocation, reporting);** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	Cocaine/MA abstinence rate (% UDS-)
		Systematic review: De Giorgi 2018[4] (Moderate)	"There is evidence that the combination of diverse approaches, especially CM with other interventions, is feasible and leads to better outcomes in patients with several needs." **Positive for CM+CBT** compared to CBT **@ 6 months:** Higher proportion of patients with stimulant-negative UDS at 6 months in CM+CBT Relapse Prevention vs CBT Relapse Prevention alone in patients with CUD who had achieved initial abstinence. 1 RCT, n=100: OR (95% CI) = 4.89 (1.51, 15.86), p<.01: • McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU) **No difference @ 12 months:** No difference between CM + CBT and CBT at 12 months. 1 RCT, n=100: • McKay 2010 (n=100 CoUD 2 wks IOP completed, TAU vs CBT-Relapse Prevention [CBT-RP]+TAU vs CM+TAU vs CM+CBT-RP+TAU)	
Stimulant use days	Low	Systematic review: AshaRani 2020[2] (Moderate-High)	**Positive for GCBT compared to CM + GCBT** in days of MA use (0.35, CI: 0.02, 0.68) in 1 RCT: • Reback & Shoptaw 2014 (n=257 MaUD MSM) **Low RoB**	
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 41 RCTs • **No difference** Pairwise meta-analysis	Dropout rate (% n):

			• **No difference**: 4 RCTs, 373 participants; I-squared=0% ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Petitjean 2014 (n=60 CoUD, 6 mo CM+CBT vs CBT-only) **Low RoB;** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)**	
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 43 RCTs • **No difference**. Pairwise meta-analysis • **No difference**: 4 RCTs, 373 participants; I-squared=0% ○ Epstein 2003 (n=286 CoUD & OUD in MMT, CM+TAU vs NCR+TAU vs CM+CBT+TAU vs NCR+CBT+TAU) **High RoB;** Petitjean 2014 (n=60 CoUD, 6 mo CM+CBT vs CBT-only) **Low RoB;** Rawson 2006 (n=177 CoUD/MaUD, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model) **Unclear RoB (randomization);** Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT) **Unclear RoB (allocation)** Author evaluation of the quality of mixed evidence • Confidence in trial end estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	Dropout rate (% n):
Stimulant dependence severity	Low	Systematic review: Rajasingham 2012[9] (Critically low)	In MSM with MUD "Interventions testing the efficacy of CM alongside other therapies such as CBT have proven modestly effective in reducing crystal meth dependence." • Jaffe 2007; Peck 2005; Rawson 2006; Reback 2004; Reback 2010; Roll 2006; Shoptaw 2006 (n=229 MaUD, CM+Sertraline/Placebo, Sertraline/Placebo alone); Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT)	
Outcome Importance: Important				
Stimulant craving	Low	Systematic review: Brown & DeFulio 2020[10] (Critically low)	**No difference** between CM + CBT and CBT in methamphetamine craving found in 1 study • Shoptaw 2006 (n=229 MaUD, CM+Sertraline/Placebo, Sertraline/Placebo alone)	

Behavioral treatment attendance	Low	Systematic review: Brown & DeFulio 2020[10] (Critically low)	**Positive for CM+CBT** compared to CBT**:** Attended more therapy sessions: 1 RCT • Shoptaw 2005 (n=162 MaUD MSM, CM alone vs CBT Matrix Model alone vs CM+CBT Matrix Model vs GCBT)	
Depressive symptoms	Low	Systematic review: Brown & DeFulio 2020[10] (Critically low)	**No interaction** between treatment and depressive symptoms in 1 RCT • Shoptaw 2006 (n=229 MaUD, CM+Sertraline/Placebo, Sertraline/Placebo alone)	Not co-occurring MDD
Sexual risk-taking behavior	Low	Systematic review: AshaRani 2020[2] (Moderate-High)	**Positive for CM + GCBT compared to GCBT:** "Modified GCBT + CM produced greater effects in reducing the number of sexual partners (-0.54, CI: -0.89, -0.19; -0.51, CI: -0.84, -0.18) at 26-week follow-up." 1 RCT • Reback & Shoptaw 2014 (n=257 MaUD MSM) Low RoB	
		Systematic review: Brown & DeFulio 2020[10] (Critically low)	**Positive for CM + GCBT compared to GCBT:** "a modified culturally specific cognitive behavioral therapy + contingency management intervention produced greater reductions in number of male sexual partners at the end of treatment and at follow-up than culturally specific cognitive behavioral therapy -only interventions. • Reback & Shoptaw 2014 (n=257 MaUD MSM)	

CBT vs Twelve Step Facilitation (TSF)

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ 12 weeks	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in longest duration of cocaine/meth abstinence in a network meta-analysis of 21 RCTs or pairwise meta-analysis of 1 RCT, 95 participants • Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
Continuous stimulant abstinence @ trial end	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	**No difference** in longest duration of cocaine/meth abstinence in a network meta-analysis of 25 RCTs or pairwise meta-analysis: 1 RCT, 95 participants • Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation)**	Longest duration (in weeks) of cocaine/ MA abstinence (UDS)
		Meta-analysis: Minozzi 2016[6] (Supplemental)	**No difference** in continuous abstinence: 2 RCTs, n=225, p=0.23	

			• Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **High RoB;** Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TSF) **High RoB**	
Continuous stimulant abstinence @ furthest follow-up	Moderate	Meta-analysis: Minozzi 2016[6] (Supplemental)	**Positive for CBT** compared to TSF in continuous abstinence: 1 RCT, n=51, RR 1.97 [1,3.86], p=0.05: • Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **High RoB**	
Stimulant abstinence @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 42 RCTs • **No difference** at 12 weeks • Evidence @ 12 weeks of significant local incoherence from inconsistent loops Pairwise meta-analysis • **No difference** 3 RCTs, 463 participants; I-squared=74.3%, p=0.02: o Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting);** Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TSF) **Unclear RoB (randomization, allocation, attrition)**	Cocaine/ MA abstinence rate (% UDS-)
Stimulant abstinence @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 46 RCTs • **No difference** at trial end, or furthest follow up. Pairwise meta-analysis • **No difference** 3 RCTs, 463 participants; I-squared=62.2%, p=0.071: o Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting);** Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TSF) **Unclear RoB (randomization, allocation, attrition)** Network & pairwise meta-analysis	Cocaine/ MA abstinence rate (% UDS-)

			• Confidence in trial end estimate: Very low; Study limitations: some concerns; Imprecision: major concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
Stimulant abstinence @ furthest follow-up	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 36 RCTs • **No difference** at furthest follow up. Pairwise meta-analysis • **No difference** 3 RCTs, 463 participants; I-squared=54.4%, p=0.112: o Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting);** Maude-Griffin 1998 (n=128 CoUD, 12 wk group CBT vs TSF) **Unclear RoB (randomization, allocation, attrition)**	Cocaine/ MA abstinence rate (% UDS-)
Treatment retention @ 12 weeks	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 41 RCTs • **Positive for CBT** compared to TSF: OR (95% CI) = 1.87 (1.22, 2.86), p=n.r. Pairwise meta-analysis • **No difference**: 2 RCTs, 335 participants; I-squared=28.2%, p=0.238: o Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting)**	12-week dropout rate (%n):
Treatment retention @ trial end	Low	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis of 43 RCTs • **Positive for CBT** compared to TSF: OR (95% CI) = 1.82 (1.16, 2.85), p=0.009. Pairwise meta-analysis • **No difference**: 2 RCTs, 335 participants; I-squared=14.2%, p=0.28: o Carroll 1998 (n=122 CoUD & AUD, 12 wk CBT-RP vs TSF vs CBT-RP+Disulfiram vs TSF+Disulfiram vs TAU+Disulfiram, TAU=Clinical Mgmt) **Unclear RoB (randomization, allocation);** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual	12-week dropout rate (%n):

			drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting)** Network & pairwise meta-analysis • Confidence in trial end estimate: Low; Study limitations: some concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	
		Meta-analysis: Minozzi 2016[6] (Supplemental)	**No difference** in dropout rate (%n): 1 RCT, n=145, p=0.45: • Schottenfeld 2011 (n=145 CoUD women, 6 mo CM+CRA vs NCR+CRA vs CM+TSF vs NCR+TSF) **High RoB**	Cochrane Review

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CBT vs Meditation-Based Treatments

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Stimulant abstinence	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis at 12 weeks (42 RCTs), trial end (46 RCTs), or furthest follow up (32 RCTs) • **No difference** at 12 weeks, trial end, or furthest follow up. Confidence in trial end estimate: Very low Pairwise meta-analysis • **No difference** 1 RCT, 104 participants: ○ Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB**	Cocaine/ MA abstinence rate (% UDS-) ACT= Acceptance and Commitment Therapy
Treatment retention	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	Network meta-analysis at 12 weeks (41 RCTs) or trial end (43 RCTs) • **No difference** at 12 weeks or trial end. Confidence in trial end estimate: Very low Pairwise meta-analysis • **No difference**: 1 RCT, 104 participants: ○ Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB**	12-week dropout rate (%n):

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

CBT vs Other

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence @ trial end	Moderate	Meta-analysis: Minozzi 2016[6] (Supplemental)	CBT vs Interpersonal Therapy (IPT) **No difference** in continuous abstinence: 1 RCTs, n=42, p=0.12 • Carroll 1991 (n=42 CoUD/use, 12 wk CBT-RP vs IPT) **High RoB**	

Stimulant abstinence rate	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	CBT vs Supportive Expressive Psychodynamic Therapy (SEPT)
			• Network meta-analysis
			  o **No difference** at 12 weeks (42 RCTs), trial end (46 RCTs), or furthest follow up (32 RCTs)
			  o Evidence @ 12 weeks of significant local incoherence from inconsistent loops
			• Pairwise meta-analysis
			  o **No difference** 1 RCT, 243 participants:
			  ▪ Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting)**
			• Author evaluation of the quality of mixed evidence at trial end
			  o Confidence in estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected
				Cocaine/ MA abstinence rate (% UDS-)

		Meta-analysis: Minozzi 2016[6] (Supplemental)	CBT vs Acceptance and Commitment Therapy (ACT)
			• **No difference** in abstinence @ end of treatment: 1 RCT, n=26, p=0.62:
			  o Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB**
			• **No difference** in abstinence @ longest follow-up: 1 RCT, n=19, p=0.55:
			  o Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB**
			
			CBT vs Interpersonal Therapy (IPT)
			  o **No difference** in abstinence @ end of treatment: 2 RCTs, n=285, p=0.72
				Cochrane Review

			○ Carroll 1991 (n=42 CoUD/use, 12 wk CBT-RP vs IPT) **High RoB** ; Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB** ○ **No difference** in abstinence @ longest follow-up: 1 RCTs, n=243, p=0.73 ○ Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB** <u>CBT vs Individual Counseling</u> ○ **Positive for CBT** compared to individual counseling in abstinence @ end of treatment: 1 RCT, n=240, RR 0.7 [0.54,0.9], p=0.01 ○ Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB** ○ **No difference** in abstinence @ longest follow-up: 1 RCT, n=240, p=0.37 ○ Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB**	
Stimulant use	Low	Systematic review: AshaRani 2020[2] (Moderate-High)	<u>CBT vs Acceptance and Commitment Therapy (ACT)</u>: ○ **No difference** between CBT and ACT in MA use (toxicology-assessed and self-reported) in one study ○ Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB**	Attrition was 70% at 12 weeks and 86% at 24 weeks.
Treatment retention	Moderate	Meta-analysis: De Crescenzo 2018[1] (High)	<u>CBT vs Supportive Expressive Psychodynamic Therapy (SEPT)</u> ○ Network meta-analysis ○ **No difference** at 12 weeks (41 RCTs) or trial end (43 RCTs). Confidence in trial end estimate: Moderate ○ Pairwise meta-analysis ○ **No difference** 1 RCT, 243 participants: ▪ Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **Unclear RoB (reporting)** ○ Author evaluation of the quality of mixed evidence at trial end ○ Confidence in estimate: Moderate; Study limitations: no concerns; Imprecision: some concerns; Heterogeneity: no concerns; Incoherence: no concerns; Indirectness: no concerns; Publication bias: undetected	12-week dropout rate (%n):

		Meta-analysis: Minozzi 2016[6] (Supplemental)	CBT vs Acceptance and Commitment Therapy (ACT) ▪ **No difference** in dropout rate (%n): 1 RCT, n=104, p=0.61: o Smout 2010 (n=104 MaUD/use, 3 mo CBT vs ACT) **High RoB** CBT vs Interpersonal Therapy (IPT) ▪ **No difference** in dropout rate (%n): 2 RCTs, n=285, p=0.45: o Carroll 1991 (n=42 CoUD/use, 12 wk CBT-RP vs IPT) **High RoB;** Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB** CBT vs Individual Counseling ▪ **No difference** in dropout rate (%n): 1 RCT, n=240, p=0.07: o Crits-Cristoph 1999 (n=487 CoUD, 6 mo CBT+TAU vs SEPT+TAU vs Individual drug counseling+TAU vs TAU=Group drug counseling/TSF) **High RoB**	Cochrane Review
Outcome Importance: Important				
Drug use	N/A	Meta-analysis: Tran 2021[11] (Supplemental)	**Positive for combined multiple psychosocial therapies compared to CBT alone:** Combined multiple psychosocial therapies reduced drug use (number of days using drugs in prior 30 days) by 1.51 days more days than those in the CBT group alone (studies = 7, n = 868, 95% CI −2.36 to −0.67, p<.001; I-squared=26%, p=0.24). ▪ Carrico 2014; Carrico 2015; Landovitz 2012; Reback 2014; Shoptaw 2005	ATStUD

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Epstein 2003[12] (Supplemental) 12 weeks 24, 52 week follow-up MMT	RCT	**(1) CM+TAU** **(3) CM+CBT+TAU:** (not Matrix Model) **(2) NCR+TAU** **(4) NCR+CBT+TAU**	n=286 CoUD & OUD	**Retention:** NSD between groups **Duration of cocaine abstinence**: Longer in CM groups than NCR groups @ 12 weeks. **Cocaine abstinence (UDS)**: Higher in CM groups than NCR groups @ 12 weeks. No significant differences between groups @ 24 and 52 weeks. CBT effects emerged after treatment.	

		TAU=Standard MMT			
Rawson 2006[5] (Supplemental)	RCT 2-week screening period 16 weeks 17-, 26- & 52-week follow-up USA Outpatient	**(1) CM alone:** Voucher-based (2) **CBT Matrix Model alone** (3) **CM+CBT** Matrix Model	N=177 (24% female) adults with CoUD (n=160) or MaUD (n=17) and active MA use during the 2-week screening period	**Continuous stimulant abstinence:** Significant treatment effect for % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial ($\chi2$=15.5, df=2,n=177, p<0.0001). ▪ CM alone > CBT alone (60% vs 34.5%; $\chi2$=14.9, df=1,n=97p<0.0001) ▪ CM+CBT > CBT alone (69.5% vs 34.5%; $\chi2$=18.4, df=1, n=97, p<0.0001) ▪ NSD between CM+CBT and CM **Stimulant abstinence** (UDS): Significant treatment effect for number of stimulant-negative urine samples collected during the trial (F=10.0, df=2, n=176, p< 0.0001). Post-hoc comparisons: ▪ CM alone > CBT alone (M=27.6 v 15.5, p=0.0008) ▪ CM+CBT > CBT alone (M=28.6 v 15.5, p=0.0003) ▪ NSD between CM+CBT and CM alone **Stimulant abstinence rate** (UDS): NSD between groups in % stimulant-negative urine samples collected at 17-, 26- & 52-week follow-up. **Duration of treatment:** Significant treatment effect on weeks in treatment. (F=6.4, df=2, n=176, p<0.01), ▪ CM > CBT alone (M=12.6 vs 9, p=0.003) ▪ CM+CBT > CBT alone (M=12 vs 9, p=0.02) ▪ NSD between CM+CBT and CM alone **Treatment completion:** Significantly lower % of participants completed treatment in CBT group ($\chi2$=8.37; p<0.02). ▪ CM alone > CBT alone (63% vs 40%) ▪ CM+CBT > CBT alone (59% vs 40%) ▪ NSD between CM+CBT and CM alone **Attendance** at CBT sessions	

				▪ CM+CBT > CBT alone (M=26.5 v 19.0, F=7.0, df=1, n=116, p< 0.01). **Other outcomes:** ASI	
Reback & Shoptaw 2014[13] (Supplemental)	Meta-analysis of 3 trials: Shoptaw 2005; 2008 and current study *Trial 1 & 2:* RCT *Trial 3:* Pre-post open-label *Trial 1:* 16 wks *Trial 3:* 8 wks 26-week follow-up USA Outpatient	***(Trial 1)* GCBT:** 16 wks Gay-specific Matrix Model CBT 3 sessions/wk from Shoptaw 2005 ***(Trial 2)* GCBT:** arm from Shoptaw 2008 ***(Trial 3)* CM+GCBT**: low-cost CM + 8 wks G-CBT 3 sessions/wk	N=257 treatment-seeking adult (18-65) MaUD MSM *Trial 1*: GCBT arm n=40 *Trial 2*: GCBT arm n=46 *Trial 3*: n=171	**Retention**: NSD between groups **Continuous stimulant abstinence:** Longest consecutive negative urine samples (weeks) ▪ GCBT (trial 1) > CM+GCBT (trial 3) in consecutive weeks of MA abstinence at the end of treatment (SMD -0.44, CI: -0.79, -0.09). NSD @ week 26. **Stimulant abstinence rate** (% UDS-neg): NSD between groups at the end of treatment or @ week 26. **Stimulant use**: Self-reported days of MA use in previous 30 ▪ GCBT (trial 2) > CM+GCBT (trial 3) in number of days of MA use at the end of treatment (SMD 0.35, CI: 0.02, 0.68) **Sexual risk-taking behavior**: ▪ CM+GCBT (trial 3) > GCBT (trial 1) in number of male sexual partners at the end of treatment (SMD -0.36, CI: -0.71, -0.02) and @ week 26 (SMD -0.54, CI: -0.89, -0.19). CM+GCBT (trial 3) > GCBT (trial 2) in number of male sexual partners @ week 26 (SMD -0.51, CI: -0.84, -0.18). NSD at treatment end.	In AshaRani 2020[2] and Knight 2019[14] "The original GCBT produced more and mostly short-term beneficial drug use outcomes, though sexual behavior changes consistently favored the modified GCBT+CM. On balance, most benefits are retained with the modified GCBT+CM intervention." (p. 1) SMD=Standardized mean difference
Shoptaw 2005[8] (Supplemental)	RCT 16 weeks 6 & 12-month follow-up USA Outpatient	**(1) CM alone:** Voucher-based CM escalation w/ reset 3 UDS/wk (n=42) **(2) CBT Matrix Model alone**: Group format (n=40) **(3) CM+CBT Matrix Model** (n=40)	N=162 treatment-seeking MSM with MaUD (61% HIV+, 80% White). Exclusions for pre-existing medical or psychiatric conditions	**Retention:** 80% at 6 months **Duration of treatment**: Significant effect of intervention on mean weeks in treatment (CBT=8.9, CM=12, CM+CBT=13.3, GCBT=11.3; F=3.78, df=3,158, p < .02). Post-hoc analysis: ▪ CM > CBT (M=12 vs 8.9, p < .05) ▪ CM+CBT > CBT (M=13.3 vs 8.9, p < .05) ▪ No difference between CM+CBT and CM alone **Attendance**: % of total possible sessions (CBT=41%, CM=32%, CBT+CM=74%, GCBT=56%). Incorporating	In Pantalone 2020[15] and Colfax 2010[16]

		(4) GCBT: Gay-Specific CBT integrating relevant cultural aspects of MA use by gay and bisexual men with Matrix Model CBT (Rawson et al., 1995). Included skills for reducing sexual risk behaviors. Group format 3 sessions/wk (n=40))		CM with CBT significantly increased attendance at therapy sessions over standard CBT. **Continuous stimulant abstinence** (UDS): Significant effect of intervention on longest period (in weeks) of consecutive MA metabolite-negative samples during the trial (CBT=2.1, CM=5.1, CM+CBT=7, GCBT=3.5; F=11.08, df=3,158, $p < .001$). Post hoc comparisons showed CM and the CM+CBT conditions averaging periods of documented abstinence over twice (CM) and three times (CM+CBT) as long as CBT. ▪ CM > CBT (M=5.1 vs 2.1, $p < .001$) ▪ CM+CBT > CBT (M=7 vs 2.1, $p < .001$) ▪ NSD between CM+CBT and CM alone ▪ NSD between GCBT and CBT Matrix Model **Stimulant abstinence rate** (UDS): Significant effect of intervention on % MA-negative urine samples collected during the trial ($\chi2$ (3) = 8.10, $p < .05$). Longitudinal model showed CBT provided fewer MA-neg samples than other three conditions (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; $\chi2$=10.03, df=1, $p < .01$). ▪ CM > CBT ▪ CM+CBT > CBT ▪ NSD between CM+CBT and CM alone ▪ NSD between groups at 6- or 12-mo follow-up ▪ Across groups, significant reduction at the end of treatment from baseline in % UDS MA+ (48% vs 17%, McNemars Q = 18.69, $p < .0001$), which was sustained at 6- and 12-month follow-ups. **Sexual risk behavior**: NSD between groups in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners at end of treatment or follow-up; significant reduction at the end of treatment in all groups for both measures, which were sustained at 6- and 12-month follow-ups.	

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT vs TAU: Small favoring CBT Some evidence that CBT is superior to TAU on stimulant use during the trial and follow-up and treatment retention, but not superior on longest duration of continuous stimulant abstinence or study endpoint stimulant use. CBT vs CRA: No differences CBT vs Other: None Most studies show no differences with other evidence-based interventions. CM+CBT vs CBT: The combination of CM+CBT is consistently superior to CBT only on most outcomes.		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT vs TAU: None CBT vs CM: None CBT vs CRA: None CBT vs Other: None CM+CBT vs CBT: None		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT vs TAU: Somewhat favors CBT CBT vs CRA: Favors neither CBT vs Other: Favors neither		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
CBT vs TAU: Moderate CBT vs CRA: Low CBT vs Other: Moderate moderate to high since numerous RCTs and meta-analyses have been done.		☐ No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	The main outcomes are highly valued across different groups CBT vs TAU: CBT vs CM: No CBT vs CRA: CBT vs Other: CM+CBT vs CBT: Probably no	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No.
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Not directly addressed by research	Common sense would argue if minoritized communities have greater harm from StUD, successful treatment should reduce health inequity, but remains to be demonstrated. Wider use of CBT in underfunded populations would likely reduce health inequities, as it appears to be superior to TAU on at least some substance use outcomes.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
EtD studies do not address this directly; would expect key stakeholders would accept	CBT is considered acceptable to all stakeholders.	☐ No ☐ Probably no ☐ Uncertain

		☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	In practice, it is widely used, so feasibility of probably yes. CBT is a somewhat resource intensive intervention, given that the availability of highly trained therapists is needed. However, the fact that CBT can be delivered in group sessions makes it more feasible for many programs.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Some evidence supports CBT as superior to usual treatment options, such as individual and group counseling, on stimulant use and abstinence outcomes during treatment and at follow-up, as well as for treatment retention. However, CBT has not been found to be superior to usual treatment options for longest duration of continuous stimulant abstinence or stimulant use at study endpoint.

Subgroup Considerations

None known.

Implementation Considerations

- Individual level implementation
  - Clinicians should consider a patient's age, sex, gender identity, race, ethnicity, sexual orientation, and other sociocultural factors that may impact their stimulant use when choosing or designing a treatment or recovery plan. Refer to the Health Disparities section for additional guidance.
- Program level
  - The CGC suggests using an evidence-based CBT manual. These are evidence-based and user-friendly: Project MATCH, NIDA CBT (Carroll), VA CBT-SUD Manual
  - Clinicians should be trained in CBT delivery to ensure fidelity

Research Priorities

- Implementation barriers for CBT

References

1. De Crescenzo F, Ciabattini M, D'Alò GL, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. Degenhardt L, ed. *PLoS Med*. 2018;15(12):e1002715. doi:10.1371/journal.pmed.1002715
2. AshaRani PV, Hombali A, Seow E, Ong WJ, Tan JH, Subramaniam M. Non-pharmacological interventions for methamphetamine use disorder: a systematic review. *Drug Alcohol Depend*. 2020;212:108060. doi:10.1016/j.drugalcdep.2020.108060
3. Harada T, Tsutomi H, Mori R, Wilson DB. Cognitive-behavioural treatment for amphetamine-type stimulants (ATS)-use disorders. *Cochrane Database Syst Rev*. 2018;12:CD011315. doi:10.1002/14651858.CD011315.pub2
4. De Giorgi R, Cassar C, Loreto D'alò G, et al. Psychosocial interventions in stimulant use disorders: a systematic review and qualitative synthesis of randomized controlled trials. *Riv Psichiatr*. 2018;53(5):233-255. doi:10.1708/3000.30003
5. Rawson RA, McCann MJ, Flammino F, et al. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. *Addiction*. 2006;101(2):267-274. doi:10.1111/j.1360-0443.2006.01312.x
6. Minozzi S, Saulle R, De Crescenzo F, Amato L. Psychosocial interventions for psychostimulant misuse. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 29, 2016. doi:10.1002/14651858.CD011866.pub2
7. Farronato NS, Dürsteler-Macfarland KM, Wiesbeck GA, Petitjean SA. A systematic review comparing cognitive-behavioral therapy and contingency management for cocaine dependence. *J Addict Dis*. 2013;32(3):274-287. doi:10.1080/10550887.2013.824328
8. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134. doi:10.1016/j.drugalcdep.2004.10.004
9. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. A Systematic Review of Behavioral and Treatment Outcome Studies Among HIV-Infected Men Who Have Sex with Men Who Abuse Crystal Methamphetamine. *AIDS Patient Care STDS*. 2012;26(1):36-52. doi:10.1089/apc.2011.0153
10. Brown HD, DeFulio A. Contingency management for the treatment of methamphetamine use disorder: A systematic review. *Drug Alcohol Depend*. 2020;216:108307. doi:10.1016/j.drugalcdep.2020.108307
11. Tran MTN, Luong QH, Le Minh G, Dunne MP, Baker P. Psychosocial Interventions for Amphetamine Type Stimulant Use Disorder: An Overview of Systematic Reviews. *Front Psychiatry*. 2021;12:512076. doi:10.3389/fpsyt.2021.512076
12. Epstein DH, Hawkins WE, Covi L, Umbricht A, Preston KL. Cognitive-behavioral therapy plus contingency management for cocaine use: Findings during treatment and across 12-month follow-up. *Psychol Addict Behav*. 2003;17(1):73-82. doi:10.1037/0893-164X.17.1.73
13. Reback CJ, Shoptaw S. Development of an Evidence-based, Gay-specific Cognitive Behavioral Therapy Intervention for Methamphetamine-abusing Gay and Bisexual Men. *Addict Behav*. 2014;39(8):1286-1291. doi:10.1016/j.addbeh.2011.11.029
14. Knight R, Karamouzian M, Carson A, et al. Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine: A systematic review. *Drug Alcohol Depend*. 2019;194:410-429. doi:10.1016/j.drugalcdep.2018.09.023
15. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
16. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *Lancet*. 2010;376(9739):458-474. doi:10.1016/S0140-6736(10)60753-2

Table 4. Matrix Model

Recommendation: The following three interventions have the most supportive evidence and are preferred alongside contingency management: CRA, CBT, and **the Matrix Model.**

Clinical Question Summary Table

Clinical Question	1. Is the Matrix Model an effective and appropriate treatment for StUD? 2. Is the Matrix Model more effective than other behavioral treatments for StUD? 3. Does adding Contingency Management to the Matrix Model improve outcomes for StUD? 4. What additional considerations and implementation strategies may influence the effects of the Matrix Model?
Population	Patients with stimulant use disorder
Intervention	Matrix Model
Comparison	Treatment as usual
Main Outcomes	Stimulant abstinence, treatment retention
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	The Matrix Model is a protocolized approach to CBT which includes additional elements of...
Abbreviations	**ASI:** Addiction Severity Index, **CBT:** Cognitive Behavioral Therapy, **CM**: Contingency Management, **DSM**: **MA:** Methamphetamine, **MAU:** Meth/Amphetamine users, **MaUD:** Methamphetamine use disorder, **Mo:** Month, **N:** Number, **NSD**: No significant difference **RoB:** Risk of Bias, **SUD**: Substance Use Disorder, **TAU**: Treatment as usual, **UDS:** Urine drug screen, **Wk**: Week
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Tables

Matrix Model CBT vs Control/TAU

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Continuous stimulant abstinence	Critical	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**Positive for Matrix Model CBT:** Matrix Model CBT associated with longer periods of MA abstinence during treatment compared to TAU (Individual Counseling)	

Stimulant use @ trial end	Critical	Low	Quasi-experimental RCT: Amiri 2016[3] n=24 MaUD men	**Positive for Matrix Model CBT:** Matrix Model CBT group showed greater reduction in MA use amount (grams/day) at 12 weeks compared to wait-list control group (MD=1.97 vs 0.59, F=4.33, df=1,22, p=0.049, d=0.16).	
Stimulant abstinence during trial	Critical	Low	Systematic review: AshaRani 2020[4] (Moderate-High)	**Author conclusion:** "Matrix model is promising, however the overall ROB score is 'High' for all included studies" (p. 16). **4 Included studies: 4 positive effects** 2. Rawson 2004 & 1-year follow-up Rawson 2008 (RCT, n=978 MaUD); Marinelli-Casey 2008 (Cohort comparison, n=287 MaUD); Amiri 2016 (Quasi-experimental RCT, n=24 MaUD men)	
			RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**Positive for Matrix Model CBT:** Matrix Model CBT participants 31% more likely to have MA-neg urine test results during treatment compared to TAU (Individual Counseling) participants (OR 1.31).	
Stimulant abstinence @ follow-up	Critical	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**No significant difference** between Matrix Model CBT and TAU (Individual Counseling) in % MA-neg samples @ 6 months (69% overall).	
Injection drug use @ trial end	Critical	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**No significant difference** between Matrix Model CBT and TAU (Individual Counseling). Overall decrease in % of sample who injected MA in past 30 days @ discharge (n=784, 14.6% vs 5.4%)	
Injection drug use @ follow-up	Critical	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**No significant difference** between Matrix Model CBT and TAU (Individual Counseling). Overall decrease in number of times injected in past 30 days @ 36 months (n=569, 17.1% to 4.4%)	
Risky sexual behavior @ trial end	Important	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**No significant difference** between Matrix Model CBT and TAU (Individual Counseling). Overall decrease in number of times having unprotected sex in the past month @ discharge months (n=784, 14.7 v 13.2, $p<0.05$).	
Risky sexual behavior @ follow-up	Important	Low	RCT: Rawson 2004[1], 2008[2] n=978 MaUD	**No significant difference** between Matrix Model CBT and TAU (Individual Counseling). Overall decrease in number of risky sex behaviors in past month @ 36 months (n=569, 24.5 v 12.8, $p<0.05$)	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Matrix Model CBT vs CM

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Continuous stimulant abstinence	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM alone:** Higher % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial compared to Matrix Model CBT alone (60% vs 34.5%; χ^2=14.9, df=1, n=97, p<0.0001)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM alone:** Longer longest period (in weeks) of consecutive MA metabolite-negative samples during the trial compared to Matrix Model CBT alone (mean=5.1 vs 2.1, p < .001)	
Stimulant abstinence during trial	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM alone:** Higher number of stimulant-negative urine samples collected during the trial compared to Matrix Model CBT alone (mean=27.6 v 15.5, p=0.0008)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM alone:** Higher % MA-negative urine samples collected during the trial compared to Matrix Model CBT alone (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; χ^2 = 10.03, df=1, p<0.01).	
Stimulant abstinence @ follow-up	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**No significant difference** between groups in % stimulant-negative urine samples collected @ 17-, 26- & 52-week follow-up.	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**No significant difference** between CM alone and Matrix Model CBT alone in % stimulant-negative urine samples collected @ 6- or 12-mo follow-ups.	
Duration of treatment	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM alone:** More average weeks in treatment compared to Matrix Model CBT alone (mean=12.6 vs 9, p=0.003)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM alone:** More average weeks in treatment compared to Matrix Model CBT alone (mean=12 vs 8.9, p<0.05)	
Treatment completion	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM alone:** Higher % of participants completing treatment compared to Matrix Model CBT alone (63% vs 40%)	
Risky sexual behavior	Important	Low	RCT: Shoptaw 2005[6] n=162 MaUD MSM	**No significant difference** between CM alone and Matrix Model CBT alone groups. Across groups, overall reduction in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners @ end of treatment, 6-, and 12-month follow-ups.	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

CM+Matrix Model CBT vs Matrix Model CBT

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Continuous stimulant abstinence	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM + Matrix Model CBT:** Higher % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial compared to Matrix Model CBT alone (69.5% vs 34.5%; χ^2=18.4, df=1, n=97, p<0.0001)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM + Matrix Model CBT:** Longer longest period (in weeks) of consecutive MA metabolite-negative samples during the trial compared to Matrix Model CBT alone (mean=7 vs 2.1, p<0.001)	
Stimulant abstinence during trial	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM + Matrix Model CBT:** Higher number of stimulant-negative urine samples collected during the trial compared to Matrix Model CBT alone (mean=28.6 v 15.5, p=0.0003)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM + Matrix Model CBT:** Higher % MA-negative urine samples collected during the trial compared to Matrix Model CBT alone (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; χ^2=10.03, df=1, p<0.01).	
Stimulant abstinence @ follow-up	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**No significant difference** between CM + Matrix Model CBT and Matrix Model CBT alone in % stimulant-negative urine samples collected @ 17-, 26- & 52-week follow-up.	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**No significant difference** between CM + Matrix Model CBT and Matrix Model CBT alone in % stimulant-negative urine samples collected @ 6- or 12-mo follow-ups	
Duration of treatment	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM + Matrix Model CBT:** More average weeks in treatment compared to Matrix Model CBT alone (mean=12 vs 9, p=0.02)	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM + Matrix Model CBT:** More average weeks in treatment compared to Matrix Model CBT alone (mean=13.3 vs 8.9, p<0.05)	
Treatment completion	Critical	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM + Matrix Model CBT:** Higher % of participants completing treatment compared to Matrix Model CBT alone (59% vs 40%)	
Session attendance	N/A	Low	RCT: Rawson 2006[5] n=177 CoUD/MaUD	**Positive for CM + Matrix Model CBT:** Higher number of sessions attended compared to Matrix Model CBT alone (mean=26.5 v 19.0, F=7.0, df=1, n=116, p< 0.01).	
			RCT: Shoptaw 2005[6] n=162 MaUD MSM	**Positive for CM + Matrix Model CBT:** Higher % of total possible sessions attended compared to Matrix Model CBT alone (CBT=41%, CM=32%, CBT+CM=74%, GCBT=56%). Incorporating CM with	

				CBT significantly increased attendance at therapy sessions over standard CBT.	
Risky behavior	Important	Low	RCT: Shoptaw 2005[6] n=162 MaUD MSM	**No significant difference** between CM + Matrix Model CBT and Matrix Model CBT alone. Across groups, overall reduction in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners @ end of treatment, 6-, and 12-month follow-ups.	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Amiri 2016[3] (Supplemental)	RCT quasi-experimental 12 weeks Iran Outpatient	**(1) CBT Matrix Model**: 12 sessions 1/wk **(2) Wait-list control**	N=24 men with MaUD (DSM-IV-TR) referred to SUD treatment. Excluded history or past or present major psychiatric disorder (psychosis, major depressive disorder, severe anxiety disorder, SUD other than MaUD, cognitive developmental disorder, severe physical or cognitive disorder, taking methadone or naltrexone.	**MA use (self-report, grams/day):** Matrix Model CBT group showed greater reduction in MA use at 12 weeks compared to wait-list control group (MD=1.97 vs 0.59, F=4.33, df=1,22, p=0.049, d=0.16). NSD between groups in baseline use.	AshaRani 2020[4]: High RoB
Marinelli- Casey 2008[7]; secondary analysis of Rawson 2004[1] (Supplemental)	Cohort comparison 16 weeks 6 & 12 month follow-up USA Outpatient	**(1) Drug Court CBT Matrix Model:** Received treatment at the drug court site (n=57) **(2) Non-Drug Court Matrix Model CBT** Received treatment at one of four other sites with patient characteristics and	N=287 adults MaUD (DSM-IV) receiving intensive outpatient Matrix Model CBT treatment for MaUD with or without drug court supervision.	Non-drug court participants had significantly higher % IDU (22.2% v 7.4%), more mean days of MA use in the past month at baseline (12.6 v 8.7), and fewer Latino participants (16.1% v 36.8%). **MA abstinence (UDS-):** More MA-neg samples provided by drug court participant during treatment (8.51 vs 5.98, p<0.001). **Treatment duration (weeks):** Longer in drug court participants (11.2 vs 7.8, F=12.33, p<0.001)	AshaRani 2020[4]: High RoB Drug court participation during Matrix Model CBT IOP treatment was associated with

		drug use patterns similar to those of the drug court group. Some with current legal system involvement (ie, on probation), but not under supervision. (n=230) All participants weekly urine drug screen.		**Treatment completion (%):** Higher in drug court participants (56.1 vs 31.7, $X^2 = 11.72$, $p<0.001$) **Other outcomes:** Self-report Addiction Severity Index (ASI) MA use score and psychosocial functioning	better treatment outcomes compared to treatment without drug court supervision.
Rawson 2004[1], 2008[2] (Supplemental)	RCT 16 weeks 6, 12, & 36-month follow-up USA, 8 sites in in Montana, Hawaii and California Outpatient	**(1) CBT Matrix Model:** 16 weeks of 3/week group sessions, including cognitive-behavioral, family education, social support, individual counseling, urine drug testing (Obert 2000). **(2) TAU:** Individual counselling sessions of variable intensity (1-3/week) and duration (8, 12, or 16 weeks). All participants weekly urine drug screen.	N=978 treatment-seeking adults with MaUD (DSM-IV) who used MA in the month before treatment entry	**Follow-up response rate:** 80% at discharge, 89% 6 months, 90% 12 months, 60% 36 months **Continuous stimulant abstinence (UDS-):** Matrix Model CBT associated with longer mean periods of MA abstinence compared to TAU. **MA abstinence (UDS-):** Matrix Model CBT participants were 31% more likely to have MA-neg urine test results during treatment compared to TAU participants (OR 1.31). NDS between groups in % MA-neg samples at 6 months (69% overall). **Treatment duration (weeks):** Matrix Model CBT group stayed in treatment longer. Matrix Model CBT participants are 38% more likely to stay in treatment compared to TAU participants (OR 1.38) **Treatment completion (%):** Matrix Model CBT participants were more likely to complete treatment than TAU participants (40.9% vs 34.2%, $X^2 = 4.68$; $p=0.031$). Matrix Model CBT participants were 27% more likely to complete treatment (OR 1.27). **Attendance:** Matrix Model CBT group attended more sessions. **Risky drug use activities** 3. NSD between groups. 4. Significant decrease in % of sample who injected MA in past 30 days @ discharge (n=784, 14.6% vs 5.4%) 5. Among injectors, significant decrease in number of times injected in past 30 days @ discharge (n=128, 19.7 v 7.8, $p<0.001$)	AshaRani 2020[4]: High RoB

				6. Significant decrease in number of times injected in past 30 days @ 36 months (n=569, 17.1% to 4.4%) **Risky sexual behavior:** • NSD between groups. • Significant decrease in number of times having unprotected sex in the past month @ discharge months (n=784, 14.7 v 13.2, $p<0.05$) • Significant decrease in number of risky sex behaviors in past month @ 36 months (n=569, 24.5 v 12.8, $p<0.05$) Reduced injection and sexual risk behaviors was significantly associated with time in treatment and treatment completion. **Other outcomes:** Self-report MA use (ASI)	
Rawson 2006[5] (Supplemental)	RCT 16 weeks 17-, 26- & 52-week follow-up Outpatient	**(1) CM alone:** Voucher-based contingency management (2) **Matrix Model CBT alone** (3) **CM+CBT Matrix Model**	N=177 (24% female) adults with CoUD (n=160) or MaUD (n=17) and active MA use during the 2-week screening period	**Continuous stimulant abstinence:** Significant treatment effect for % of participants achieving 3 or more consecutive weeks of stimulant abstinence during the trial (χ^2=15.5, df=2, n=177, $p<0.0001$). • CM alone > CBT alone (60% vs 34.5%; χ^2=14.9, df=1, n=97$p<0.0001$)) • CM+CBT > CBT alone (69.5% vs 34.5%; χ^2=18.4, df=1, n=97, $p<0.0001$) • NSD between CM+CBT and CM **Stimulant abstinence**: Significant treatment effect for number of stimulant-negative urine samples collected during the trial (F=10.0, df=2, n=176, p< 0.0001). Post-hoc comparisons: • CM alone > CBT alone (M=27.6 v 15.5, $p=0.0008$) • CM+CBT > CBT alone (M=28.6 v 15.5, $p=0.0003$) • NSD between CM+CBT and CM alone	

				Stimulant abstinence rate: NSD between groups in % stimulant-negative urine samples collected at 17-, 26- & 52-week follow-up. **Duration of treatment:** Significant treatment effect on weeks in treatment (F=6.4, df=2, n=176, p<0.01), • CM > CBT alone (M=12.6 vs 9, p=0.003) • CM+CBT > CBT alone (M=12 vs 9, p=0.02) • NSD between CM+CBT and CM alone **Treatment completion:** Significantly lower % of participants completed treatment in CBT group (χ^2=8.37; p<0.02). • CM alone > CBT alone (63% vs 40%) • CM+CBT > CBT alone (59% vs 40%) • NSD between CM+CBT and CM alone **Attendance** at CBT sessions • CM+CBT > CBT alone (M=26.5 v 19.0, F=7.0, df=1, n=116, p< 0.01). **Other outcomes**: ASI	
Shoptaw 2005[6] (Supplemental)	RCT 2 week baseline period 16 week trial 6 & 12-month follow-up USA Outpatient	**(1) CM alone:** Voucher-based CM escalation w/ reset 3 UDS/wk (n=42) **(2) Matrix Model CBT alone**: Group format (n=40) **(3) CM+Matrix Model CBT** (n=40) **(4) GCBT**: Gay-Specific CBT integrating relevant cultural aspects of MA use by gay and bisexual men with Matrix Model CBT (Rawson et al., 1995). Included skills for reducing sexual risk behaviors. Group format 3 sessions/wk (n=40))	N=162 treatment-seeking MSM with MaUD (61% HIV+, 80% White). Exclusions for pre-existing medical or psychiatric conditions	**Retention:** 80% at 6 months **Duration of treatment**: Significant effect of intervention on mean weeks in treatment (CBT=8.9, CM=12, CM+CBT=13.3, GCBT=11.3; F=3.78, df=3,158, p<0.02). Post-hoc analysis: • CM > CBT (M=12 vs 8.9, p<0.05) • CM+CBT > CBT (M=13.3 vs 8.9, p<0.05) • NSD between CM+CBT and CM alone • NSD between G-CBT and other conditions **Attendance**: % of total possible sessions (CBT=41%, CM=32%, CBT+CM=74%, GCBT=56%). Incorporating CM with CBT significantly increased attendance at therapy sessions over standard CBT. **Continuous stimulant abstinence** (UDS): Significant effect of intervention on longest period (in weeks) of consecutive MA metabolite-negative	AshaRani 2020[4]: High RoB

				samples during the trial (CBT=2.1, CM=5.1, CM+CBT=7, GCBT=3.5; F=11.08, df=3,158, p<0.001). Post hoc comparisons showed CM and the CM+CBT conditions averaging periods of documented abstinence over twice (CM) and three times (CM+CBT) as long as CBT. • CM > CBT (M=5.1 vs 2.1, p<0.001) • CM+CBT > CBT (M=7 vs 2.1, p<0.001) • NSD between CM+CBT and CM alone • NSD between G-CBT and other conditions **Stimulant abstinence rate** (UDS): Significant effect of intervention on % MA-negative urine samples collected during the trial (χ^2 = 8.10, df=3, p<0.05). Longitudinal model showed CBT provided fewer MA-neg samples than other three conditions (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; χ^2 = 10.03, df=1, p<0.01). • CM > CBT • CM+CBT > CBT • NSD between CM+CBT and CM alone • NSD between groups at 6- or 12-mo follow-up • Across groups, significant reduction at the end of treatment from baseline in % UDS MA+ (48% vs 17%, McNemars Q = 18.69, p<0.0001), which was sustained at 6- and 12-month follow-ups. **Sexual risk behavior**: NSD between groups in self-reported incidence of unprotected anal intercourse and number of prior 30-day sexual partners at end of treatment or follow-up. Across groups, significant reduction at the end of treatment in all groups for both measures, which were sustained at 6- and 12-month follow-ups.	

ASI: Addiction Severity Index (McLellan, A.T., Kushner, H., & Metzger, D., Peters, R., Smith et al., 1992).
Texas Christian University (TCU) AIDS Risk Assessment (Simpson, Camacho, Vogtsberger, Williams, Stephens et al., 1994)

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
The Matrix Model produced greater reductions in methamphetamine use in two studies with TAU or a wait list control group (Shoptaw 2005[6], Rawson 2006[5], Amiri 2016[3]). The Matrix model also reduced craving and risky behavior compared to waitlist control (AshaRani 2020[4] Systematic Review).	Only three studies of the Matrix Model fit review inclusion criteria	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
None reported		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Given the positive effects on methamphetamine use and lack of negative effects, the balance favors the Matrix Model.	Somewhat favors since based on three studies not since replicated (since 2006).	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
A small number of controlled studies of the Matrix Model yields low confidence, but study quality is high. Balance = moderate.	Moderate in the context of StUD research	☐ No included studies ☐ Very low ☐ Low ☒ Moderate

		☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence found in systematic review.	The main outcomes that were examined—methamphetamine use, abstinence, craving, and risky behavior—are valued.	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence found in systematic review.	Providing greater access to the Matrix Model in underserved populations will reduce health inequities. However, due to lack of direct evidence, will say probably. Also, research priority should be evaluating cultural appropriateness for specific minority populations.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Is widely used.	The Matrix Model does not present major problems in acceptability.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
Is widely used.	The Matrix Model is compatible with the structure and staffing at many SUD treatment programs and has been widely adopted, supporting it being a feasible option. It does require staff training.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes

		☐ Varies

Conclusions

Justification

Practically speaking this approach is most widely-adopted among formalized treatment programs of StUD. Three studies comparing Matrix Model CBT to wait list or TAU show reduced methamphetamine use. Shoptaw 2005[6] and Rawson 2006[5] show additional benefit of addition of contingency management to Matrix Model CBT. The Rawson study is the only one to address CoUD; all others MaUD.

Subgroup Considerations

None known.

Implementation Considerations

- Individual level implementation considerations -Adapt treatment for each patient
  - Clinicians should consider a patient's age, sex, gender identity, race, ethnicity, sexual orientation, and other sociocultural factors that may impact their stimulant use when choosing or designing a treatment or recovery plan. Refer to the Health Disparities section for additional guidance.
- Program level
  - Assess staffing needs and network of providers
  - Staff training prior to implementation

Research Priorities

- Evaluating cultural appropriateness for specific minority populations.

References

1. Rawson RA, Marinelli-Casey P, Anglin MD, et al. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction*. 2004;99(6):708-717. doi:10.1111/j.1360-0443.2004.00707.x
2. Rawson RA, Gonzales R, Pearce V, et al. Methamphetamine dependence and human immunodeficiency virus risk behavior. *J Subst Use Addict Treat*. 2008;35(3):279-284. doi:10.1016/j.jsat.2007.11.003
3. Amiri Z, Mirzaee B, Sabet M. Evaluating the efficacy of regulated 12-session Matrix Model in reducing susceptibility in methamphetamine-dependent individuals. *Int J Med Res Health Sci*. 2016;5(2):77-85.
4. AshaRani PV, Hombali A, Seow E, Ong WJ, Tan JH, Subramaniam M. Non-pharmacological interventions for methamphetamine use disorder: a systematic review. *Drug Alcohol Depend*. 2020;212:108060. doi:10.1016/j.drugalcdep.2020.108060
5. Rawson RA, McCann MJ, Flammino F, et al. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. *Addiction*. 2006;101(2):267-274. doi:10.1111/j.1360-0443.2006.01312.x
6. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134. doi:10.1016/j.drugalcdep.2004.10.004
7. Marinelli-Casey P, Gonzales R, Hillhouse M, et al. Drug court treatment for methamphetamine dependence: Treatment response and posttreatment outcomes. *J Subst Use Addict Treat*. 2008;34(2):242-248. doi:10.1016/j.jsat.2007.04.005

Technology-Based Interventions

Table 5. Computer-Delivered Treatment

Recommendation: Clinicians can consider offering evidence-based behavioral interventions delivered via digital therapeutics or web-based platforms as add-on components to treatment for StUD, but they should not be used as standalone treatment.

Clinical Question Summary Table

Clinical Question	1. What is the effect of computer-delivered treatment for stimulant use disorder? 2. What contextual factors and implementation strategies may influence the effects of computer-delivered treatment?
Population	Patients with stimulant use disorder
Intervention	Computer delivered interventions (including internet/web-based and app-based interventions) as primary or adjunct treatment
Comparison	In person intervention (Treatment as usual)
Main Outcomes	Stimulant use, treatment retention
Setting	SUD specialty treatment, Virtual/Home/Community
Background & Definitions	Notes: • What is computer delivered tx? How is it different from in-person intervention? • Why would we expect it to be a beneficial intervention for StUD patients? • **Therapeutic Education System (TES)**: is a Web-based community reinforcement approach (CRA) learning program developed by HealthSim, LLC designed for patients in opiate-replacement treatment by Bickel et al. (2008)[1]. Patients are exposed to short (10–12 minutes) learning modules and then tested on timed recognition and recall tasks with feedback until they overlearn core concepts. • **CBT4CBT**: 6-session computer-based training in cognitive–behavioral therapy • **Snow Control**: Online CBT- and MI-based intervention for cocaine users. Eight modules in the first 3 weeks, with 4 additional voluntary modules that can be accessed during weeks 4 to 6. • **breakingtheice**: Online CBT- and MI-based intervention for amphetamine-type stimulant (ATS) users. 3 self-guided modules. • **e-learning Serigaya Methamphetamine Relapse Prevention Program (e-SMARPP)**: A 6 module online relapse prevention program. • **EMA app**
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CBT**: Cognitive Behavioral Therapy, **CoUD**: Cocaine use disorder, **CM:** Contingency management, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MMT**: Methadone maintenance therapy, **N**: Number, **NSD**: No significant difference, **OPT**: Outpatient treatment, **OR**: Odds ratio, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **SUD**: Substance use disorder, **TAU**: Treatment as usual, **UDT**: Urine drug test

Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Evidence Profile Table

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant Use	Moderate	Non-systematic review: Rubenis 2021[2] (Supplementary)	No significant effect of **web-based interventions** for MA and similar stimulants on ATS use in 2 RCTs. • *Tait 2015* (n=160 out-of-treatment ATS users, Online CBT for ATS 'breakingtheice' vs Wait-list) NSD; *Takano 2020* (n=48 SUD [MA 57%] in OPT, Online relapse prevention CBT for MA 'e-SMARPP' vs Control) NSD	"Low levels of engagement with interventions might have masked the true treatment effect in both studies" (p. 4)
		Meta-analysis: Boumparis 2017[3] (High)	No significant difference between **web-based interventions** and control conditions on stimulant use reduction (4 studies, 481 participants, Hedge's g=0.13, 95% CI –0.05 to 0.31, p=0.164). • *Tait 2015* (n=160 out-of-treatment ATS users, Online CBT for ATS 'breakingtheice' vs Wait-list) NSD; *Brooks 2010* (n=28 CoUD in treatment, TES+CM+TAU vs NCR+TAU) NSD; *Carroll 2014* (n=101 CoUD in MMT, CBT4CBT+TAU vs TAU) **Favors CBT4CBT;** *Schaub 2012* (n=196 out-of-treatment cocaine users, Online CBT for cocaine 'Snow Control' vs Control) NSD	
		RCT: Takano 2020[4]	No significant difference between online relapse prevention for MA (**'e-SMARPP'**) and Control on relapse risk or duration of abstinence from primary drug in 48 SUD (57% MA) outpatients.	In Rubenis 2021[2] SR
		RCT: Reback 2018[5]	No significant difference between **EMA app** and EMA app+Counseling in MA use at 12 weeks in 136 MSM in outpatient tx who used MA in past year.	
		RCT: Tait 2015[6]	No effect of online CBT for ATS use (**'breakingtheice'**) on ATS use at three months compared to Wait-list control in 160 out-of-treatment ATS users.	In Rubenis 2021[2] SR and Boumparis 2017[3] meta-analysis
		RCT: Carroll 2014[7]	**CBT4CBT+TAU** more likely to attain three or more consecutive weeks of cocaine abstinence than TAU alone (36% vs 17%, OR=0.36, p<0. 05).	In Boumparis 2017[3] meta-analysis

			6 month follow up indicated continued treatment gains. N=101, CoUD in methadone maintenance therapy.	
		RCT: Schaub 2012[8]	No significant difference between Online CBT for cocaine (**'Snow Control'**) and Online control in 196 out-of-treatment cocaine users.	In Boumparis 2017[3] meta-analysis
		RCT: Brooks 2010[9]	No significant difference between **TES+CM+TAU** and NCR+TAU in cocaine use in 28 CoUD outpatients. NCR = Non-conditional reward	In Boumparis 2017[3] meta-analysis
Treatment completion	Moderate	RCT: Kiluk 2018[10]	**CBT4CBT** group had higher treatment retention compared to in-person CBT or TAU. Effect size? N=137 SUD (29% cocaine) outpatients.	
		RCT: Tait 2015[6]	No significant difference between Online CBT for ATS use (**'breakingtheice'**) and Wait-list Control in retention at 6 months in 160 out-of-treatment ATS users.	Overall attrition rate 51% at 6 months.
		RCT: Campbell 2014[11]	**TES+TAU** participants less likely to dropout than in TAU (Hazard Ratio 0.72, 95% CI 0.57 to 0.92, p=0.01) N=507 SUD (34% primary stimulant users) outpatients.	
		RCT: Carroll 2014[7]	No significant difference between **CBT4CBT+TAU** and **TAU** groups	
		RCT: Schaub 2012[8]	**Online CBT for cocaine ('Snow Control')** group had higher retention than Online Control group at 5 weeks in 196 out-of-treatment cocaine users (18.8% vs 8%, OR 2.65, 95% CI 1.04-6.77, p=0.04)	
		RCT: Carroll 2008[12]	No significant difference between **CBT4CBT+TAU** and **TAU** groups	
Help seeking	Low	RCT: Tait 2015[6]	**Online CBT for ATS use ('breakingtheice')** had higher actual help seeking behavior compared to Wait-list **Control** at 6 months (RR 2.16, d=0.45) among 160 out-of-treatment ATS users.	
Treatment motivation	Moderate	RCT: Tait 2015[6]	**Online CBT for ATS use ('breakingtheice')** had more participants transition to the action stage of change compared to Wait-list **Control** (OR 4.13, 95% CI 1.03-16.58) among 160 out-of-treatment ATS users.	
		RCT: Takano 2020[4]	No significant difference between **online MA relapse prevention program ('e-SMARPP')** and **Control** groups in motivation to change in 48 SUD (57% MA) outpatients.	Two-thirds of participants had been in treatment for longer than a year.
Important Outcomes				
Drug use	N/A	RCT: Kiluk 2018[10]	No significant difference between **CBT4CBT** and clinician CBT; both associated with reduced substance use. However only CBT4CBT showed sustained effects over 6 months. N=137 SUD (29% cocaine) outpatients.	Standalone CBT4CBT
		RCT: Campbell 2014[11] and Cochran 2015[13]	**TES+TAU** was associated with increased drug and heavy alcohol abstinence compared to TAU in the final four weeks of treatment, but not at 3- and 6-month follow-ups. The effect was driven by treatment response among participants with a positive baseline drug test and among primary **stimulant** users. Among primary stimulant users, TES+TAU group had higher odds of end of treatment abstinence than TAU group when controlling for baseline abstinence (60.5% vs 47.3%, aOR 3.59,	Not stimulant specific, but effect strongest in primary stimulant users.

			95% CI 1.25-10.27, p=0.017). N=507 SUD (34% primary stimulant users) outpatients.	
Drug use	N/A	RCT: Carroll 2008[12] and Carroll 2009[14]	**CBT4CBT+TAU** associated with lower rate of drug use during the trial compared to TAU alone. Effect was strongest for rate of cocaine use (28% vs 44%). The effect remained significant 1 month after trial end, but not at further follow-up points. N=77 (58% CoUD) in outpatient SUD treatment	Effectiveness of intervention driven by quality of coping skills obtained (mediation analysis).
Adverse events	N/A	RCT: Kiluk 2018[10]	No adverse events appeared to be related to **CBT4CBT**	
		RCT: Schaub 2012[8]	No significant difference between Online CBT for cocaine **('Snow Control')** and Online **Control** groups in rate of contacting outpatient treatment services for additional help in 196 out-of-treatment cocaine users.	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Systematic Reviews and Meta-Analysis Findings Table

Outcome	SOE[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant Use	Moderate	Non-systematic review: Rubenis 2021[2] (Supplementary)	**No significant effect** of web-based interventions for MA and similar stimulants on MA use in 2 studies. "Low levels of engagement with interventions might have masked the true treatment effect in both studies" (p. 4)	
		Meta-analysis: Boumparis 2017[3] (High)	**No significant difference** between internet intervention vs control conditions on stimulant use reduction (4 studies, 481 participants, Hedge's g=0.13, 95% CI –0.05 to 0.31, p=0.164).	
Treatment seeking	Moderate	Non-systematic review: Rubenis 2021[2] (Supplementary)	**Web-based intervention** increased informal help-seeking in a largely (90%) treatment naïve sample.	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Systematic Reviews and Meta-Analyses

Study	Design	Outcomes	Evidence
Boumparis 2017[3]	**Design:** Meta-analysis **Quality:** High **Population:** Substance use **Intervention(s):** Tech-based between internet intervention vs control conditions	**Stimulant Use** No significant difference between internet intervention vs control conditions on stimulant use reduction (4 studies, 481 participants, Hedge's g=0.13, 95% CI –0.05 to 0.31, p=0.164).	**Tait 2015** (n=160 out-of-treatment ATS users, Online CBT for ATS 'breakingtheice' vs Wait-list) NSD; **Brooks 2010** (n=28 CoUD in treatment, TES+CM+TAU vs NCR+TAU) NSD; **Carroll 2014** (n=101 CoUD in MMT, CBT4CBT+TAU vs TAU) Favors CBT4CBT; **Schaub 2012** (n=196 out-of-treatment cocaine users, Online CBT for cocaine 'Snow Control' vs Control) NSD
Rubenis 2021[2]	**Design:** Non-systematic review Supplementary **Intervention(s):** Web-based intervention stimulants	**Stimulant Use** No significant effect of web-based interventions for MA and similar stimulants on MA use in 2 studies. "Low levels of engagement with interventions might have masked the true treatment effect in both studies" (p. 4)	**Tait 2015** (n=160 out-of-treatment ATS users, Online CBT for ATS 'breakingtheice' vs Wait-list) NSD ; **Takano 2020** (n=48 SUD [MA 57%] in OPT, Online relapse prevention CBT for MA 'e-SMARPP' vs Control) NSD
		Treatment Seeking: Intervention increased informal help-seeking in a largely (90%) treatment naïve sample.	**Tait 2015** (n=160 out-of-treatment ATS users, Online CBT for ATS 'breakingtheice' vs Wait-list)

Primary Review: Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Campbell 2014[11]; Cochran 2015[13] RoB: High	RCT 12 wk duration, 6 mo follow-up Country: Outpatient SUD	**TES + TAU**: TAU and Therapeutic Education System (TES) substituted for approximately two hours of usual in-person counseling. TES also included a CM intervention for module completion and negative drug tests. **TAU**	N=507 **substance** abuse patients. 34% primary stimulant users. Substance dependence: 35% cocaine, 20% stimulant	**Drug and heavy drinking abstinence (**UDS & self-report): Higher odds of abstinence in TES group compared to TAU at the end of treatment (OR=1.62 [1.12, 2.35], p=0.01). Significant interaction: TES group had higher odds of abstinence than TAU group among participants with a baseline positive test (n= 275, OR 2.18, 95% CI 1.30-3.68, p=0.003), but NSD among participants with a baseline negative test (p=0.489). NSD between groups at 3- and 6-month follow-ups. **End of treatment abstinence**: Significant interaction: Among primary stimulant users, TES group had higher odds of drug (UDS) and heavy alcohol (self-report) abstinence in the final four weeks of treatment than TAU group when controlling for baseline abstinence (60.5% vs	Supports TES as an adjunct to outpatient TAU for stimulant users

				47.3%, aOR 3.59, 95% CI 1.25-10.27, p=0.017). NSD among primary alcohol, cannabis, or opioid users. **Treatment retention:** Participants in TES less likely to dropout than TAU participants (Hazard Ratio=0.72, 95% CI 0.57-0.92, p=0.01)	
Reback 2018[15]	RCT 8 wk duration, 4 wk follow-up USA Outpatient SUD	**(1) EMA app:** Ecological Momentary Assessments for Self-Monitoring **(2) EMA app + 1-to-1 counselling** **(3) Historical controls:**	N=136 MSM who used **MA** in past 12 months	**MA use** (UDS & self-report): NSD between groups at 12 wks	In Rubenis 2021[2]
Schwartz 2014[16] RoB: Low	RCT 3-mo follow-up USA Primary care	**(1) Computer BI:** **(2) In-person BI**: delivered by a behavioral health counselor	N=360 primary care patients with a **substance**-specific moderate-risk ASSIST score (4-26). Prevalence in sample: cocaine (n=66), amphetamines or methamphetamines (n=40)	**Meth/ amphetamine use (hair test)**: NSD in % of cocaine or amphetamine-positive har tests between groups at 3 months. **Drug risk (ASSIST)**: NSD in Global ASSIST drug score between groups at 3 months. **Cocaine risk (ASSIST):** Scores lower in CBI than IBI group at 3 months (n=66, MD −4.48, 95% CI −8.26 to −0.71; Cohen's d=.50; p=.021) **Meth/ amphetamine risk (ASSIST):** NSD in score between groups at 3 months (n=40)	ASSIST risk: patterns of use and problems related to use

ASI = Addiction Severity Index
ASSIST
BDI = Beck Depression Inventory
CCQ-Brief = Cocaine Craving Questionnaire Brief
SDS = Severity of Dependence Scale

Supplemental Review: Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Campbell 2014[11]; Cochran 2015[13]	RCT 12 wk duration, 6 mo follow-up Country: Outpatient SUD	**TES + TAU**: TAU and Therapeutic Education System (TES) substituted for approximately two hours of usual in-person counseling. TES also included a CM intervention for module completion and negative drug tests. **TAU**	N=507 **substance** abuse patients. 34% primary stimulant users. Substance dependence: 35% cocaine, 20% stimulant	**Drug and heavy drinking abstinence (**UDS & self-report): Higher odds of abstinence in TES group compared to TAU at the end of treatment (OR=1.62 [1.12, 2.35], p=0.01). Significant interaction: TES group had higher odds of abstinence than TAU group among participants with a baseline positive test (n= 275, OR 2.18, 95% CI 1.30-3.68, p=0.003), but NSD among participants with a baseline negative test	Supports TES as an adjunct to outpatient TAU for stimulant users

				(p=0.489). NSD between groups at 3- and 6-month follow-ups. **End of treatment abstinence**: Significant interaction: Among primary stimulant users, TES group had higher odds of drug (UDS) and heavy alcohol (self-report) abstinence in the final four weeks of treatment than TAU group when controlling for baseline abstinence (60.5% vs 47.3%, aOR 3.59, 95% CI 1.25-10.27, p=0.017). NSD among primary alcohol, cannabis, or opioid users. **Treatment retention:** Participants in TES less likely to dropout than TAU participants (Hazard Ratio=0.72, 95% CI 0.57-0.92, p=0.01)	
Carroll 2008[12] and Carroll 2009[14]	RCT 8 wk duration, 1, 3 & 6 mo follow-up USA Outpatient SUD	**(1) CBT4CBT + TAU:** biweekly access at clinic **(2) TAU**: weekly individual and group sessions of general drug counseling	N=77 **substance** use disorder (58% current cocaine use disorder)	6 month follow-up rate 82% Quality of coping skills obtained mediated the effect of the intervention on outcomes **Cocaine use** (UDS): Lower rate of cocaine-positive urine tests for CBT4CBT+ TAU than TAU during the study (28% vs 44%). **Drug use** (UDS): CBT4CBT associated with lower rate of drug-positive urine tests during the study (34% vs 53%, F=3.9, p=0.05, d=0.46). CBT4CBT more likely to submit a drug-negative sample at the 1-month follow-up (76% vs 48%, F=3.9, p=.05), but not at the 3- or 6-month follow-up. **Longest continuous abstinence** (self-report drug/alcohol): NSD between groups during the study (22 vs 14 days, p=0.07, d=0.45). CBT4CBT reported longer periods of consecutive abstinence during the follow-up period (102 vs 72.5 days, F=3.9, p=0.05). **Treatment retention**: NSD between groups (22/39 vs 26/38).	Overall attrition rate 22%
Kiluk 2017[17]					Did not replicate this finding in pts with CoUD in methadone maintenance

Kiluk 2018[10]	RCT 1, 3 & 6 mo follow-up USA Outpatient SUD, Virtual	**(1) CBT4CBT+Monitoring**: Delivered with minimal (brief weekly) clinical monitoring **(2) In-person CBT:** Delivered weekly by a clinician on an individual basis **(3) TAU**: Weekly group and/or individual therapy	N=137 treatment-seeking outpatients with current substance abuse or dependence (DSM-IV-TR) (29% cocaine use)	**Substance use**: Both CBT4CBT and clinician CBT associated with reduced substance use compared to TAU. Only CBT4CBT showed sustained effects over 6 months. **Treatment retention**: Highest in CBT4CBT group compared to clinician CBT or TAU. **Treatment satisfaction:** Highest in CBT4CBT group compared to clinician CBT or TAU.	First study of CBT4CBT as standalone tx
Reback 2018[15]	RCT 8 wk duration, 4 wk follow-up USA Outpatient SUD	**(1) EMA app:** **(2) EMA app and one-to-one counsellor:** **Historical controls:**	N=136 MSM who used **MA** in past 12 months	**MA use** (UDS & self-report): NSD between groups at 12 wks	In Rubenis 2021[2]
Schwartz 2014[16]	RCT 3-mo follow-up USA Primary care	**(1) Computer BI:** **(2) In-person BI**: delivered by a behavioral health counselor	N=360 primary care patients with a **substance**-specific moderate-risk ASSIST score (4-26). Prevalence in sample: cocaine (n=66), amphetamines or methamphetamines (n=40)	**Meth/ amphetamine use (hair test)**: NSD in % of cocaine or amphetamine-positive har tests between groups at 3 months. **Drug risk (ASSIST)**: NSD in Global ASSIST drug score between groups at 3 months. **Cocaine risk (ASSIST):** Scores lower in CBI than IBI group at 3 months (n=66, MD −4.48, 95% CI −8.26 to −0.71; Cohen's d=.50; p=.021) **Meth/ amphetamine risk (ASSIST):** NSD in score between groups at 3 months (n=40)	ASSIST risk: patterns of use and problems related to use

ASI = Addiction Severity Index
ASSIST
BDI = Beck Depression Inventory
CCQ-Brief = Cocaine Craving Questionnaire Brief
SDS = Severity of Dependence Scale

Studies in SRs and MAs: Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Reviews
Brooks 2010[9]	RCT 8 wk duration, 2 wk follow-up USA Outpatient SUD	**(1) TES+CM+TAU**: Therapeutic Education System 3 sessions/week at research lab + cash incentive for completing modules **(2) NCR+TAU**: Yoked payments All participants received standard outpatient treatment.	N=28 new outpatients who attended for 1 week, with **cocaine** abuse or dependence (DSM 4), and report cocaine as a primary drug of choice. Randomization was stratified on baseline positive UDT for cocaine use.	In Boumparis 2017[3]

Carroll 2014[7]	RCT 8 wk duration, 9 mo follow-up USA Outpatient SUD	**(1) CBT4CBT+TAU**: 7 modules **(2) TAU:** Methadone maintenance therapy (MMT)	N=101 co-occurring **cocaine** and opioid dependence in MMT	In Boumparis 2017[3]
Schaub 2012[8]	RCT 6 wk duration, 6 mo follow-up Switzerland Community	**(1) Online CBT:** CBT-based intervention 'Snow Control' **(2) Control:** Online psychoeducation about cocaine matched in duration and intensity. All participants received 24-hour contact information for study staff and emergency help and local outpatient clinic contact information.	N=196 out-of-treatment adult **cocaine** users reporting use ≥ 3 times in the past 30 days recruited via online and offline media. Exclusion criteria included participation in other treatments for cocaine use, prior 30 day opioid use except for substitution therapy, and history of cardiovascular problems or apoplexy. Average of 6.7 years (sd=6.9) of cocaine use.	In Boumparis 2017[3] High overall attrition rate 85%
Tait 2015[6]	RCT 3 & 6-mo follow-up Australia Community	**(1) Online CBT for ATS:** Access to 3 modules of self-guided online CBT- and MI-based intervention for amphetamine-type stimulant (ATS) users ('breakingtheice'). 48% of intervention group completed all 3 modules, 36% did not complete any modules. **(2) Control:** Wait-list	N=160 out-of-treatment adults self-reporting use of **ATS** in the previous 3 months recruited via social network sites and posters in local clinics (75.6% male).	In Rubenis 2021[2] and Boumparis 2017[3] Overall attrition rate 51% at 6 months.
Takano 2020[4]	RCT 8 wk duration Japan Outpatient SUD	**(1) Online CBT for MA:** 6 module online relapse prevention program e-learning Serigaya Methamphetamine Relapse Prevention Program ('e-SMARPP') based on CBT Matrix Model. 74% of e-SMARPP group completed the program. **(2) Control**: Self-monitoring component of e-SMARPP only	N=48 patients already in outpatient treatment for non-alcohol or tobacco **substance** use disorder (MA, 57%; all others, <15%) and internet access. Two-thirds of participants had been in treatment for longer than a year	In Rubenis 2021[2] Also in Continuing care Participants likely continued to receive OPT during the intervention

ASI = Addiction Severity Index
ASSIST
BDI = Beck Depression Inventory
CCQ-Brief = Cocaine Craving Questionnaire Brief
SDS = Severity of Dependence Scale

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
While a small meta-analysis found no effect across 4 web-based interventions on stimulant use, a few individual studies of particular interventions effectively reduced substance use, particularly cocaine. Less evidence of efficacy for amphetamine and methamphetamine use. There was only 1 study found that examined CBT4CT as a standalone treatment, and while positive, this is insufficient evidence to recommend it as a standalone treatment at this time. CBT4CBT and TES appear to improve stimulant use outcomes during treatment or at end of treatment when added to other behavioral interventions. However, these effects are no longer evident at post-treatment follow-ups. These interventions may be similarly effective to clinician delivered CBT/treatment, however there is less evidence on this. No consistent effect on treatment retention.	One study suggested the positive effect of TES was greater in those with a drug positive urine test at baseline. While evidence is strongest for cocaine use, the CDC has no reason to believe it would be significantly different for ATS use.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No specific evidence of harms found in the literature review.	Some concern over use of computer delivered interventions as standalone interventions. Some patients who really need more intensive treatment may opt for this approach because they believe it will be more convenient. Also, the lack of a clinician could make it more difficult to identify decompensating behavior, and catch warning signs and red flags like suicidal thoughts/behavior.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*

The balance of effects favors the interventions since there are no known undesirable effects, particularly with TES and CBT4BT.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
The certainty/quality of the evidence is low, due to a small number of studies, small sample sizes in most cases, and effects that do not persist past the end of treatment.		☐ Clinical judgment ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	The main outcomes of stimulant use and retention are highly valued	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	Wider use of these interventions could make effective treatment available to many who cannot regularly attend clinic based treatment. This issue has become even more important during covid. However, use of these interventions typically requires access to high-speed internet and a smart phone or computer, which are not available to many people.	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		

Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	Some individuals will be unfamiliar with the technology used to deliver these interventions, or will not want to do treatment virtually	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	The cost is unknown, but is expected to be expensive. High speed internet access and smart phones/computers are not available to many individuals. Insurance generally does not cover these services. RESET	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Observed effect of randomized trials The Clinical Guideline Committee (CGC) considered the body of literature on computer-delivered treatment assessed in the literature review; the evidence suggests moderate to large reductions in substance use. Despite a lack of evidence relating to Population Y, the CGC considered the principles of Intervention A as applicable to Population Y. The CGC envisaged the importance of the future wider availability of Population Y and anticipated that policies on reimbursement will be updated. The CGC reached a consensus that the overall balance of effects favors Intervention A, particularly with consideration of acceptability and financial sustainability to government authorities, patients and the community.

Subgroup Considerations

None known.

Implementation Considerations

If implementing

- Computer and high-speed internet access
- Computer literacy

References

1. Bickel WK, Marsch LA, Buchhalter AR, Badger GJ. Computerized behavior therapy for opioid-dependent outpatients: A randomized controlled trial. *Exp Clin Psychopharmacol*. 2008;16(2):132-143. doi:10.1037/1064-1297.16.2.132

2. Rubenis AJ, Baker AL, Arunogiri S. Methamphetamine use and technology-mediated psychosocial interventions: A mini-review. *Addict Behav*. 2021;121:106881. doi:10.1016/j.addbeh.2021.106881
3. Boumparis N, Karyotaki E, Schaub MP, Cuijpers P, Riper H. Internet interventions for adult illicit substance users: A meta-analysis. *Addiction*. 2017;112(9):1521-1532. doi:http://dx.doi.org.pitt.idm.oclc.org/10.1111/add.13819
4. Takano A, Miyamoto Y, Shinozaki T, Matsumoto T, Kawakami N. Effect of a web-based relapse prevention program on abstinence among Japanese drug users: A pilot randomized controlled trial. *J Subst Use Addict Treat*. 2020;111:37-46. doi:10.1016/j.jsat.2019.12.001
5. Reback C, Rünger D, Fletcher JB, Swendeman D. Ecological momentary assessments for self-monitoring and counseling to optimize methamphetamine treatment and sexual risk reduction outcomes among gay and bisexual men. *J Subst Use Addict Treat*. 2018;92:17-26. doi:10.1016/j.jsat.2018.06.005
6. Tait RJ, McKetin R, Kay-Lambkin F, et al. Six-Month Outcomes of a Web-Based Intervention for Users of Amphetamine-Type Stimulants: Randomized Controlled Trial. *J Med Internet Res*. 2015;17(4):e105. doi:10.2196/jmir.3778
7. Carroll KM, Kiluk BD, Nich C, et al. Computer-assisted delivery of cognitive-behavioral therapy: Efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. *Am J Psychiatry*. 2014;171(4):436-444. doi:10.1176/appi.ajp.2013.13070987
8. Schaub M, Sullivan R, Haug S, Stark L. Web-based cognitive behavioral self-help intervention to reduce cocaine consumption in problematic cocaine users: randomized controlled trial. *J Med Internet Res*. 2012;14(6):e166. doi:10/gj7qwc
9. Brooks AC, Ryder D, Carise D, Kirby KC. Feasibility and effectiveness of computer-based therapy in community treatment. *J Subst Use Addict Treat*. 2010;39(3):227-235. doi:10.1016/j.jsat.2010.06.003
10. Kiluk BD, Nich C, Buck MB, et al. Randomized Clinical Trial of Computerized and Clinician-Delivered CBT in Comparison With Standard Outpatient Treatment for Substance Use Disorders: Primary Within-Treatment and Follow-Up Outcomes. *Am J Psychiatry*. 2018;175(9):853-863. doi:10.1176/appi.ajp.2018.17090978
11. Campbell ANC, Nunes EV, Matthews AG, et al. Internet-Delivered Treatment for Substance Abuse: A Multisite Randomized Controlled Trial. *Am J Psychiatry*. 2014;171(6):683-690. doi:10.1176/appi.ajp.2014.13081055
12. Carroll KM, Ball SA, Martino S, et al. Computer-Assisted Delivery of Cognitive-Behavioral Therapy for Addiction: A Randomized Trial of CBT4CBT. *Am J Psychiatry*. 2008;165(7):881-888. doi:10.1176/appi.ajp.2008.07111835
13. Cochran G, Stitzer M, Campbell ANC, Hu MC, Vandrey R, Nunes EV. Web-based treatment for substance use disorders: differential effects by primary substance. *Addict Behav*. 2015;45:191-194. doi:10.1016/j.addbeh.2015.02.002
14. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Rounsaville BJ. Enduring Effects of a Computer-Assisted Training Program For Cognitive Behavioral Therapy: A six-month follow-up of CBT4CBT. *Drug Alcohol Depend*. 2009;100(1-2):178-181. doi:10.1016/j.drugalcdep.2008.09.015
15. Reback C, Rünger D, Fletcher JB, Swendeman D. Ecological momentary assessments for self-monitoring and counseling to optimize methamphetamine treatment and sexual risk reduction outcomes among gay and bisexual men. *J Subst Use Addict Treat*. 2018;92:17-26. doi:10.1016/j.jsat.2018.06.005
16. Schwartz R, Gryczynski J, Mitchell SG, et al. Computerized versus in-person brief intervention for drug misuse: a randomized clinical trial. *Addiction (Abingdon, England)*. 2014;109(7):1091-1098. doi:10.1111/add.12502
17. Kiluk BD, DeVito EE, Buck MB, Hunkele K, Nich C, Carroll KM. Effect of computerized cognitive behavioral therapy on acquisition of coping skills among cocaine-dependent individuals enrolled in methadone maintenance. *J Subst Use Addict Treat*. 2017;82:87-92. doi:10.1016/j.jsat.2017.09.011

Table 6. Telehealth

Recommendation: Clinicians should consider using telemedicine to deliver behavioral treatment for StUD to patients who may have challenges accessing in-person care.

Clinical Question Summary

Clinical Question	1. What is the effect of telehealth-delivered treatment for stimulant use disorder? 2. What contextual factors and implementation strategies may influence the effects of telehealth-delivered treatment?
Population	Patients with stimulant use disorder
Intervention	Telehealth delivery of psychosocial treatment for stimulant use disorders
Comparison	Any other treatment, In-person treatment, No treatment
Main Outcomes	Stimulant use, treatment retention
Setting	Any clinical setting, home
Background & Definitions	Notes • What is telehealth? What does it do? • Why would we expect it to be a beneficial intervention for StUD patients?
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings Table

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant use	Very low	Non-systematic review: Rubenis 2021[1] (Supplementary)	**No significant difference** between telephone vs standard aftercare in UDT-verified stimulant use in 2 reports of one study (Farabee 2013; Karno 2012)	"Mini-review"
Important Outcome				

Drug use	Very low	Non-systematic review: Rubenis 2021[1] (Supplementary))	**Telephone aftercare** group had greater improvement in ASI drug use score compared to standard aftercare at 3 months, especially among people actively using but no difference at 12 months in 2 reports of one study (Farabee 2013; Karno 2012).	Mini-review"

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Farabee 2013[2] and Karno 2012[3] (Not assessed)	RCT Duration: 12 wks, follow-up at 12 months Location: USA Setting: **Aftercare**	**Telephone counseling aftercare**: (1) unstructured non-directive; (2) structured non-directive; (3) unstructured directive; (4) structured directive (5) **Standard aftercare**	N=302 recently completed outpatient treatment for stimulant dependence. Primary drug: MA, 56%; cocaine, 30%; both, 14%	**Stimulant use** (UDD): n.s.d. between groups. **Drug use**: Decrease in ASI drug use score in telephone group compared to increase in standard group at three months (-17% vs 17%, χ (1) = 4.95, d = 0.26, p = .026). No difference at 12 months. Among those with baseline ASI score > 0 (n = 152), greater degrease in ASI drug use score in telephone compared to standard group at 3 months (34% vs 2%, χ (1) = 6.18, d = 0.41, p = .013)	Also in Continuing Care
Grigg 2022[4]	Pre-post retrospective analysis of program data Location: Australia	**Ready2Change**: A multiple-session outbound telephone-delivered CBT intervention for mild-to-moderate substance use disorders, embedded within a 24/7 alcohol and drug helpline	N=249 with alcohol (n=191), methamphetamine (n=40) or cannabis (n=18) use problems	Among methamphetamine users (n=40) **Substance use problem severity** (DUDIT): Reduced problem severity following intervention (mean difference = −17.3, 95% CI −20.9, −13.7). **Psychological distress**: Reduced psychological distress following intervention	
McKay 2005[5]	RCT Duration: 12 wks, 24 mo follow-up Location: USA Setting: **Outpatient to continuing care**	(1) **TMC**: Telephone-based monitoring and brief counseling weekly for 12 wks and weekly group for first 4 wks (2) **RP**: In-person cognitive-behavioral relapse prevention (CBT-RP) 1 individual and 1 group session per week. (3) **STND**: In-person group counseling twice per week (standard	N=359 **alcohol- and/or cocaine-**dependent patients who completed 4 weeks of intensive outpatient treatment (9 hrs/wk for 1 month). 45% cocaine dependent.	**Cocaine use** (UTD): In cocaine-dependent participants (n=, 268) there was a significant group by time interaction (p=.03) in which the rate of cocaine-positive urine samples during follow-up increased more rapidly in RP as compared with TMC. Trend toward similar interaction for STND and TMC (p=0.053). **Cocaine and alcohol abstinence**: TMC had higher rates of total abstinence over the follow-up than those in STND (p<0.05). High risk patients (co-occurring dependence, poor progress toward achieving IOP goals), had better total abstinence outcomes up to 21 months if they received STND rather than TMC, whereas low-risk patients had higher abstinence rates in TMC than in STND (p=.04).	

		outpatient continuing care).			
McKay 2010[6], 2011[7]	RCT Duration: 18 months, 12 & 24-mo follow-up Location: USA Setting: **Outpatient to continuing care**	(1) **TM**: Telephone monitoring and feedback (2) **TMC**: Telephone monitoring, feedback, and counseling All patients received intensive outpatient program (IOP) (9 hrs/wk) for 3 to 4 months then standard outpatient (1 group/week) up to 6 months total	N=252 **alcohol- and/or cocaine-**dependent patients who completed 3 weeks of intensive outpatient treatment. 49% current cocaine dependence	**Cocaine use**: Among participants with lifetime cocaine dependence (n=199), n.s.d. on rates of cocaine positive urines at 12 months. **Drug and heavy alcohol abstinence** composite: n.s.d. for whole sample over 24 months	
McKay 2013a[8]	RCT Duration: 12 months Location: USA Setting: **Outpatient to continuing care**	(1) **TAU**: Standard intensive outpatient treatment (9 hours/week of group) for 3 to 4 months then standard outpatient (1 group/week) up to 6 months total (2) **TMC + CM + TAU**: Enhanced continuing care (**ECC**)—Telephone monitoring and adaptive counseling weekly for 8 weeks then biweekly for 35 weeks and incentives for attendance.	N=152 adults entering treatment with lifetime diagnosis of **cocaine** dependence and who used cocaine in the past 6 months. Approximately 70% had current cocaine dependence, 30% current alcohol dependence.	**Cocaine use** (UDT): Rate of cocaine-positive urine samples during follow-up was *higher* in the ECC than in the TAU group, and the difference increased over time (at 12 months, 52% vs. 20%). Results were not moderated by substance use at intake or early in treatment or by IOP attendance. **Drug and heavy alcohol abstinence** (composite): Abstinence rate slightly higher in ECC than in the TAU group at 3 months (47% vs. 42%), but at 9 and 12 months higher in TAU than in ECC group.	Negative result: "most patients had stopped or greatly reduced their cocaine use in the month before treatment, and less than 30% showed evidence of cocaine use in the first month of IOP" McKay 2013a (p8)[8]
McKay 2013b[9] McCollister 2016[10] McKay 2014[11]	RCT Duration: 24-month follow-up Location: USA	(1) **TAU**: Standard intensive outpatient treatment (9 hours/week of group) for 3 to 4 months then standard outpatient (1	N=321 adults (age 18-65) with a lifetime diagnosis of **cocaine** dependence (DSM-IV) who used cocaine in the prior 6 months and who	**Cocaine use** (UDT): n.s.d between groups overall. Among participants with cocaine use at baseline (n=137), lower use rate in TMC+CM than TAU group (OR= 0.55 [0.31, 0.95], p=0.03) but not TMC vs TAU (p=0.22) or TMC vs TMC+CM (p=0.48). The size of the effect was larger in women than in men (TMC vs	Also see Prevention: Sex risk and Continuing Care NCT00685659

Mensinger 2007[12] Van Horn 2011[13]	Setting: **Outpatient to continuing care**	group/week) up to 6 months total. (2) **TMC + TAU**: Telephone monitoring and adaptive counseling weekly for 8 weeks, biweekly for 35 weeks, monthly for 6 months, bimonthly for 6 months. Approximately 20 minutes per call. (3) **TMC + CM + TAU**: Adds incentives for TMC attendance. About 20 % of patients randomized to TMC and TMC+CM failed to complete the initial orientation sessions.	completed 2 weeks of intensive outpatient treatment. Approximately 83% had current cocaine dependence, 39% had current alcohol dependence.	TAU: women = −0.69, men = −0.21; TMC+CM vs TAU: women = −0.64, men = −0.11). The size of the effect was larger in participants with low vs high readiness to change (TMC vs TAU: low = −0.51, high = −0.18; TMC+CM vs TAU: low = −0.37, high = −0.09). n.s.d between groups among cocaine abstinent participants at baseline. **Drug and heavy alcohol abstinence** (composite): n.s.d between groups overall. Among participants with cocaine use at baseline (n=137), abstinence rate higher in TMC than TAU group (OR=1.95 [1.02, 3.73], p= 0.04) but not TMC+CM vs TAU (p=0.14) or TMC vs TMC+CM (p=0.53). n.s.d between groups among participants abstinent at baseline.	Effect dependent on self-reported abstinence at intake and early in treatment (ie, within 30 days prior to the baseline assessment). Effects were larger for women and low baseline readiness to change.

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Other Resources

Source	Resource	Comments
SAMHSA 2021	In Brief: Rural Behavioral Health: Telehealth Challenges and Opportunities (https://store.samhsa.gov/product/SMA16-4989): This guide for behavioral healthcare providers describes the barriers associated with implementing telehealth services in rural and frontier communities and offers tips on how to overcome those.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*

The telehealth evidence for stimulant use disorder at this time involves audio only and is often only provided after some amount of in person care. The evidence for audio only telehealth for follow up care of individuals with cocaine use disorder is mixed, with some positive and some negative studies. There was one RCT of a mixed cocaine and MA population that found positive effects on reduced drug use, suggesting telehealth is also effective for MaUD. Video telehealth has not been studied.	The CGC presumes that video telehealth would perform similarly to audio only, though it should be tested because some patients may have discomfort with appearing on camera. While there is no evidence for earlier stages of treatment, because there are practical limitations to in-person care, if those limitations are insurmountable, telehealth treatment is preferable to no treatment at all. Most of the studies examined individual treatment. Much stimulant use disorder treatment is done via group therapy. There is no evidence about the efficacy of telehealth for group therapy.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
There was one RCT where adding telephone counseling to IOP produced worse cocaine use outcomes than IOP alone. This is one of the few studies of telehealth in the earlier stages of treatment.		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
The balance of effects favors the intervention since there are no known undesirable effects.		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*

The certainty of evidence is moderate for audio only telehealth in aftercare for cocaine use disorder since several randomized trials indicate a modest benefit.		☐ Clinical judgment ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	Patients and clinicians value a reduction in substance use.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	There could be substantial impacts on health inequities since some impoverished individuals do not even own telephones let alone the technology to do video telehealth. Also, some individuals lack private spaces in which they can maintain confidentiality while engaging in telehealth.	☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence found in the literature review.	Acceptability varies. Some patients like the convenience of telehealth. Other patients much prefer in person care. Similarly, some clinicians are very comfortable with telehealth, while others are not. Comfort level has probably generally increased during the pandemic, as more patients and clinicians have been forced to adopt telehealth.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*

No evidence found in the literature review.	As noted above telehealth technology and private spaces are not available to all patients. Other than that consideration telehealth has already been widely implemented and seems feasible generally.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusions

Justification

The balance of effects favors the intervention since there are no known undesirable effects.

Subgroup Considerations

None known.

Implementation Considerations

As noted above telehealth technology and private spaces are not available to all patients. Other than that consideration telehealth has already been widely implemented and seems feasible generally.

Research Priorities

The CGC presumes that video telehealth would perform similarly to audio only, though it should be tested because some patients may have discomfort with appearing on camera.

References

1. Rubenis AJ, Baker AL, Arunogiri S. Methamphetamine use and technology-mediated psychosocial interventions: A mini-review. *Addict Behav*. 2021;121:106881. doi:10.1016/j.addbeh.2021.106881
2. Farabee D, Cousins SJ, Brecht ML, et al. A comparison of four telephone-based counseling styles for recovering stimulant users. *Psychol Addict Behav*. 2013;27(1):223-229. doi:10.1037/a0029572
3. Karno M, Farabee D, Brecht ML, Rawson R. Patient Reactance Moderates the Effect of Directive Telephone Counseling for Methamphetamine Users. *J Stud Alcohol Drugs*. 2012;73(5):844-850. doi:10.15288/jsad.2012.73.844
4. Grigg J, Volpe I, Tyler J, et al. READY2CHANGE : Preliminary effectiveness of a telephone-delivered intervention program for alcohol, methamphetamine and cannabis use problems. *Drug Alcohol Rev*. 2022;41(2):517-527. doi:10.1111/dar.13363
5. McKay JR, Lynch KG, Shepard DS, Pettinati HM. The Effectiveness of Telephone-Based Continuing Care for Alcohol and Cocaine Dependence: 24-Month Outcomes. *Arch Gen Psychiatry*. 2005;62(2):199-207. doi:10.1001/archpsyc.62.2.199
6. McKay JR, Van Horn DHA, Oslin DW, et al. A randomized trial of extended telephone-based continuing care for alcohol dependence: within-treatment substance use outcomes. *J Consult Clin Psychol*. 2010;78(6):912-923. doi:10.1037/a0020700\
7. McKay JR, Van Horn D, Oslin D, et al. Extended Telephone-Based Continuing Care for Alcohol Dependence: 24 Month Outcomes and Subgroup Analyses. *Addiction*. 2011;106(10):1760-1769. doi:10.1111/j.1360-0443.2011.03483.x

8. McKay JR, Van Horn D, Ivey M, Drapkin ML, Rennert L, Lynch KG. Enhanced Continuing Care Provided in Parallel to Intensive Outpatient Treatment Does Not Improve Outcomes for Patients With Cocaine Dependence. *J Stud Alcohol Drugs*. 2013a;74(4):642-651. doi:10.15288/jsad.2013.74.642
9. McKay JR, Van Horn DHA, Lynch KG, et al. An adaptive approach for identifying cocaine dependent patients who benefit from extended continuing care. *J Consult Clin Psychol*. 2013b;81(6):1063-1073. doi:10.1037/a0034265
10. McCollister K, Yang X, McKay JR. Cost-effectiveness analysis of a continuing care intervention for cocaine-dependent adults. *Drug Alcohol Depend*. 2016;158:38-44. doi:10/f77k2r
11. McKay JR, Van Horn DHA, Lynch KG, et al. Who benefits from extended continuing care for cocaine dependence? *Addict Behav*. 2014;39(3):660-668. doi:10.1016/j.addbeh.2013.11.019
12. Mensinger JL, Lynch KG, TenHave TR, McKay JR. Mediators of telephone-based continuing care for alcohol and cocaine dependence. *J Consult Clin Psychol*. 2007;75(5):775-784. doi:10.1037/0022-006X.75.5.775
13. Van Horn DH, Drapkin M, Ivey M, et al. Voucher incentives increase treatment participation in telephone-based continuing care for cocaine dependence. *Drug Alcohol Depend*. 2011;114(2-3):225-228.

Pharmacotherapy

Table 7. Bupropion for Cocaine Use Disorder

Recommendation: For patients with cocaine use disorder, clinicians can consider prescribing bupropion to promote cocaine abstinence.

a. Clinicians can give bupropion additional consideration for patients with a co-occurring tobacco use disorder as this medication can also reduce nicotine/tobacco use.
b. Clinicians can give bupropion additional consideration for patients with co-occurring depression as this medication can also treat depression.

Clinical Question Summary Table

Clinical question	Is bupropion safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
Population	Patients with cocaine use disorder
Intervention	Bupropion (generic bupropion hydrochloride, brand name Wellbutrin ©)
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, adverse events, cigarette consumption
Setting	Inpatient or outpatient specialty SUD treatment
Considerations	• Co-occurring nicotine use disorder • Seizure risk (history of seizure, lower seizure threshold)
Background & Definitions	Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA-approved for the treatment of major depressive disorder (MDD), seasonal affective disorder, and smoking cessation
Abbreviations	**BID:** Twice a day, **CI:** Confidence Interval, **CoUD:** Cocaine Use Disorder, **MA**: Methamphetamine, **MaUD:** Methamphetamine Use Disorder, **N:** Number, **RCT**: Randomized Controlled Trial, **RoB:** Risk of Bias, **RR**: Risk Ratio, **SMD**: Standard Mean Difference
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Note: Chan (2019) covers the studies in Castells (2016). As it is less recent, Castells (2016) was excluded from the literature review. On review, Chan (2019) seems to report the results from Castells (2016) rather than conducting their own analysis, so the results from Castells (2016) are reported here.

Summary of Findings Table: Bupropion for CUD

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[i])[ii]	Effect/Impact	Comments
Sustained stimulant abstinence	Critical	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**Bupropion > Placebo** in higher rate of 3+ week abstinence in 2 RCTs, n=176, 36% vs 22%, RR 1.63, 95% CI 1.03-2.59, p=.04	Cochrane review: psychostimulants

				• Poling 2006 (n=106 CoUD & OUD in MMT, 25 wks 300 mg/d); Shoptaw 2008 (n=70 CoUD & not AUD, 16 wks 300 mg/d)	for cocaine dependence
Stimulant abstinence	Important	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in mean proportion of cocaine-free urinalysis across the study per patient in 2 RCTs, n=176, SMD=0.24, 95% CI -0.06 to 0.54, p=.12 • Poling 2006 (n=106 CoUD & OUD in MMT, 25 wks 300 mg/d); Shoptaw 2008 (n=70 CoUD & not AUD, 16 wks 300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Treatment retention	Critical	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in treatment completion rate in 3 RCTs, n=325, 60.7% vs 61.8%, RR 0.99, 95% CI 0.79-1.25, p=.84. • Margolin 1995 (n=149 CoUD & OUD in MMT, 12 wks 200-300 mg/d); Poling 2006 (n=106 CoUD & OUD in MMT, 25 wks 300 mg/d); Shoptaw 2008 (n=70 CoUD & not AUD, 16 wks 300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Dropout due to adverse events	Critical	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in rate of dropout due to adverse events in 1 study, n=149, 2/74 (2/5%) vs 2/75 (2.6%), RD 0, 95% CI -0.05 to 0.05, p=.99 • Margolin 1995 (n=149 CoUD & OUD in MMT, 12 wks 200-300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Dropout due to cardiovascular adverse events	Critical	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in rate of dropout due to adverse events in 1 study, n=149, 0/74 (0%) vs 0/75 (0%), RD 0, 95% CI -0.03 to 0.03, p=n/a • Margolin 1995 (n=149 CoUD & OUD in MMT, 12 wks 200-300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Cocaine craving	Important	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in cocaine craving in 2 RCTs, n=137, SMD=0.07, 95% CI –0.3 to 0.44, p=.71. • Margolin 1995 (n=149 CoUD & OUD in MMT, 12 wks 200-300 mg/d); Shoptaw 2008 (n=70 CoUD & not AUD, 16 wks 300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Depressive symptoms	Important	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in depressive symptom severity in 1 RCT, n=62, SMD= -0.04, 95% CI -0.54 to 0.46, p-.86. • Poling 2006 (n=106 CoUD & OUD in MMT, 25 wks 300 mg/d)	Cochrane review: psychostimulants for cocaine dependence
Other substance use: Heroin	Important	High	Meta-analysis: Castells 2016[1] (Supplemental)	**No difference** between bupropion and placebo in mean proportion of heroin-free UDT across the study per participant in 1 RCT, n=105, SMD= 0.29, 95% CI -0.13 to 0.71, p=.18 or in sustained heroin abstinence rate 1 RCT, n=105, 60% vs 38%, RR 1.57, 95% CI 0.78-3.15, p=.2	Cochrane review: psychostimulants for cocaine dependence

				• Poling 2006 (n=106 CoUD & OUD in MMT, 25 wks 300 mg/d)	
Other substance use: Smoking	Important	High	Systematic review: Siefried 2020[2] (High)	**Bupropion + nicotine inhaler + counseling** group had greater reduction in cigarette smoking compared to counseling alone found in 1 RCT of a mixed cocaine/meth use disorder population • Winhusen 2014 (n=538 CoUD/MaUD 10 wks 150-300 mg/d)	Mixed CoUD/MaUD population

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Evidence to Decision Table: Bupropion for CoUD

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
There is weak evidence for bupropion facilitating abstinence from cocaine use. Added benefit of reduced tobacco use in patients who smoke cigarettes or use other tobacco products.	Anticipated effects are small, but there is an absence of other options Bupropion is FDA approved for treatment of depression.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Bupropion is generally well tolerated. In studies for CoUD, there were no significant differences in dropout or adverse effects between bupropion and placebo.	Bupropion has been extensively studied for smoking cessation and other conditions like binge eating, and some adverse effects observed in these clinical trials are likely important to consider in the treatment of CoUD. Bupropion should be avoided in individuals with history of seizure or eating disorders and used with caution in individuals with elevated seizure risk.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Although both desirable and undesirable effects are small, the potential benefits outweigh the potential risks. Especially with the lack of strongly supported medication alternatives, the use of bupropion for cocaine use disorder is supported.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither

		☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Weak evidence from few studies.		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No research data to support	No important uncertainty	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
*** Equity:** What would be the impact on health inequities?		
Research Evidence	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability:** Is the option acceptable to key stakeholders?		
Research Evidence	*Additional Considerations*	*Judgment*
	At face value, outcomes and potential efficacy are likely to be acceptable to most patients, clinicians, and policymakers.	☐ No ☐ Probably no ☐ Uncertain

	Bupropion is a commonly prescribed and generally well-tolerated medication. Bupropion is a generic medication and is commonly covered by insurance and savings clubs.	☒ Probably yes ☐ Yes ☐ Varies
* **Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence	*Additional Considerations*	*Judgment*
	Bupropion is commonly used in a number of other conditions, including for depression and tobacco cessation. A generic formulation is available and is commonly available on medication formularies. It is relatively easy to titrate dosing. May not be feasible in treatment settings without staff with the ability to prescribe medication.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Especially in the context of the lack of strongly supported medication alternatives, the CGC agreed that bupropion may be considered as a pharmacotherapeutic option for cocaine use disorder

Subgroup Considerations

None noted

Implementation Considerations

- Suggested dosing
- Bupropion should be avoided in patients with elevated seizure risk.

References

1. Castells X, Cunill R, Pérez-Mañá C, Vidal X, Capellà D. Psychostimulant drugs for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database of Syst Rev*. Published online September 27, 2016. doi:10.1002/14651858.CD007380.pub4
2. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x

Table 8. Topiramate for Cocaine Use Disorder

Recommendation: For patients with cocaine use disorder, clinicians can consider prescribing topiramate to reduce cocaine use.

a. Clinicians can give topiramate additional consideration for patients with co-occurring alcohol use disorder, as it can also reduce alcohol consumption.

Clinical Question Summary Table

Clinical Question	Is topiramate safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
Population	Patients with cocaine use disorder
Intervention	Topiramate
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, adverse events, psychological symptoms, alcohol consumption
Setting	Inpatient or outpatient settings
Considerations	• Co-occurring alcohol use disorder • Co-occurring headaches • Metabolic acidosis • Concerns regarding cognition
Perspective	Individual
Background & Definitions	Topiramate is an anticonvulsant medication that is FDA-approved for the treatment of epilepsy and migraine
Abbreviations	**AUD**: Alcohol use disorder, **CoUD:** Cocaine Use Disorder, **CM:** Contingency management, **MA:** Methamphetamine, **MDS:** Medical/doctoral specialist, **N:** Number, **N/A**: Not applicable, **OUD**: Opioid use disorder, **RoB:** Risk of Bias, **RR:** Risk ratio, **SUD:** Substance use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality)[ii]	Effect/Impact	Comments
Continuous stimulant abstinence	Critical	Low	Meta-analysis: Chan 2020[1] (Moderate-High)	**No effect.** No difference in longest duration of cocaine abstinence (1 RCT, n= 171).	

				• Umbricht 2014 (n=171 w/ co-occurring OUD, 18 wks, 300 mg/day titrated over 7 wks)	
			Meta-analysis: Chan 2019[2] (Moderate)	**Positive effect for topiramate.** Higher rate of continuous 3 + weeks cocaine abstinence for topiramate vs placebo (2 RCTs, n=210, RR (95% CI) = 2.43 (1.31, 4.53), p=0.005). • Kampman 2004 (n=40, 13 wks, 200 mg/day titrated over 8 wks); Kampman 2013 (n=170, 14 wks, 300 mg/day titrated over 8 wks)	
			Meta-analysis: Singh 2016[3] (Supplemental)	**Positive effect for topiramate.** Higher rate of continuous 3 + weeks cocaine abstinence for topiramate vs placebo (2 RCTs, n=210, RR (95% CI) = 2.56 (1.39, 4.73), p=0.003). • Kampman 2004 (n=40, 13 wks, 200 mg/day titrated over 8 wks); Kampman 2013 (n=170, 14 wks, 300 mg/day titrated over 8 wks)	
Stimulant use	Critical	Low	Meta-analysis: Chan 2020[1] (Moderate-High)	**No effect.** No difference in overall % of cocaine-negative urine samples: 1 RCT, n=171, p = 0.86. • Umbricht 2014 (n=171 w/ co-occurring OUD, 18 wks, 300 mg/day titrated over 7 wks)	
Treatment retention	Critical	Low	Meta-analysis: Chan 2019[2] (Moderate)	**No effect.** No significant difference in treatment retention rate between topiramate and placebo/ no medication groups (RCTs=5, p=0.79). • Nuijten 2014 (n=142, 12 wks, CBT alone vs CBT + topiramate 200 mg/day titrated over 3 wks); Baldacara 2016 (n=60 [100% male], 12 wks, 200 mg/day titrated); Johnson 2013 (n=142, 12 wks, 300 mg/day titrated over 6 wks); Kampman 2013 (n=170, 14 wks, 300 mg/day titrated over 8 wks); Umbricht 2014 (n=171 w/ co-occurring OUD, 18 wks, 300 mg/day titrated over 7 wks)	
			Meta-analysis: Singh 2016[3] (Supplemental)	**No effect.** No significant difference in dropout rate between topiramate and placebo (RCTs=4, n=444, p=0.38). • Johnson 2013 (n=142, 12 wks, 300 mg/day titrated over 6 wks); Kampman 2004 (n=40, 13 wks, 200 mg/day titrated over 8 wks); Kampman 2013 (n=170, 14 wks, 300 mg/day titrated over 8 wks); Umbricht 2014 (n=171 w/ co-occurring OUD, 18 wks, 300 mg/day titrated over 7 wks)	

Stimulant craving	Important	Moderate	Meta-analysis: Singh 2016[3] (Supplemental)	The 5 included studies used different cocaine craving measures, so meta-analysis could not be performed. **Mixed results.** One (Johnson 2013; n = 142) out of four studies (n = 302; Kampman 2004, 2013; Umbricht 2014; Nuijten 2014) reported improvement in subjective cocaine craving scores with topiramate compared to placebo.	
Adverse events	Important	Low	Meta-analysis: Singh 2016[3] (Supplemental)	**No effect.** No difference in rate of adverse events between groups treated with topiramate vs placebo (2 RCTs, n=234, p=0.48). • Johnson 2013 (300 mg/day [titrated over 6 wks] for 12 wks, n=142); Umbricht 2014 (300 mg/day [titrated over 7 wks] for 18 wks, n=171 w/ co-occurring OUD).	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Mixed results. Substantial RR for the 2 Kampman studies that looked at abstinence outcomes, but no effect in Umbricht 2014[4], although this was with a co-occurring OUD population. No effect on treatment retention.	Topiramate is approved for migraine prophylaxis and has evidence supporting off-label treatment of AUD.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Most do not tolerate maximum doses	Known side effects of topiramate include cognitive effects and parasthesias. However, better tolerability if slow titration.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

Evidence Summary	*Additional Considerations*	*Judgment*
Weak evidence, and somewhat offset by known side effects and variable tolerability of the medication.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
*** Equity:** What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence from literature review. The 2 positive trials were primarily in URM.		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies

* **Acceptability:** Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence from literature review on non- research patient population acceptability.	Need to address how widely available physicians who feel comfortable prescribing off-label medications, particularly the access to these physicians by URM groups. However, treatment would perhaps reduce health inequities if internists, primary care MDS used these meds. Need to educate stakeholders on the need for slow titration, otherwise may have high drop-out	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
* **Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence from literature review	low cost, widely available medication, but variable familiarity by providers, and titration schedule may vary based on tolerability. But need to be trained on who it will be appropriate for and that titration needs to be slow. May be useful for those with comorbid alcohol use disorder- although less clear if it helps with AUD.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Topiramate might be considered in patients who are interested in achieving abstinence or remain abstinent if entering treatment abstinent. It may also work among those with co-morbid AUD. Although not clear that it works for those in methadone-maintenance- although this study (Umbricht) used CM which may have impacted on the findings.
One study, by Johnson, also found topirmate worked for those actively using at baseline and reduced use but need further work.
There are 2 trials that combined MAS-XR and topiramate and both found in more frequent users that abstinence was sign higher in the combined medication group but we cannot definitely say whether this improvement was due to the combination, MAS-XR or topiramate

Based on 2 Kampman trials and Umbricht study. There is another trial by Johnson where patients were active users at baseline and had a reduction of use over time and topiramate outperformed placebo but this is only 1 trial.

a. Evidence that it promotes abstinence but other measures such as retention or craving not assessed or found to be superior with topiramate. Biggest issue is sedation and cognitive impairment such that patients do not want to remain on it. Therefore, need to titrate up dose slowly.

Subgroup Consideration

Perhaps best for those who are interested in abstinence, want help with sleep, have a seizure risk. Maybe be better for more frequent users but this was found in studies where both MAS-XR and topiramate were given.

Implementation Considerations

Biggest issue is sedation and cognitive impairment such that patients do not want to remain on it. Therefore, need to titrate up dose slowly, and avoid interactions with medications that might increase metabolic acidosis.

Research Priorities

Large, multisite trial with abstinence as the main outcome. Advantage is medication is not as expensive as other SUD medication.

References

1. Chan B, Freeman M, Ayers C, et al. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. *Drug Alcohol Depend*. 2020;216:108193. doi:10.1016/j.drugalcdep.2020.108193
2. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-analysis. *J Gen Intern Med*. 2019;34(12):2858-2873. doi:10.1007/s11606-019-05074-8
3. Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a systematic review and meta-analysis of randomized controlled trials. *Addiction*. 2016;111(8):1337-1346. doi:10.1111/add.13328
4. Umbricht A, DeFulio A, Winstanley EL, et al. Topiramate for cocaine dependence during methadone maintenance treatment: A randomized controlled trial. *Drug and Alcohol Dependence*. 2014;140:92-100. doi:10.1016/j.drugalcdep.2014.03.033

Table 9. Bupropion for Amphetamine-Type Stimulant Use Disorder

Recommendation: For patients with amphetamine-type stimulant use disorder with low- to moderate-frequency of stimulant use (eg, <18 days/month), clinicians can consider prescribing bupropion to promote reduced use of amphetamine-type stimulants.

a. Clinicians can give bupropion additional consideration for patients with co-occurring TUD, as this medication can also reduce nicotine/tobacco use.
b. Clinicians can give bupropion additional consideration for patients with co occurring depressive disorders, as this medication can also treat depression.

Clinical Question Summary Table

Clinical Question	Is bupropion safe and effective at reducing stimulant use and increasing treatment retention in patients with amphetamine-type stimulant use disorder?
Population	Patients with amphetamine-type stimulant use disorder
Intervention	Bupropion (generic bupropion hydrochloride, brand name Wellbutrin ©)
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, depressive symptoms, adverse events, other substance use (nicotine)
Setting	Inpatient or outpatient specialty SUD treatment
Considerations	• Co-occurring nicotine use disorder • Seizure risk (history of seizure, lower seizure threshold)
Background & Definitions	Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA-approved for the treatment of major depressive disorder (MDD), seasonal affective disorder, and smoking cessation Doses used effectively include sustained-release 150 mg twice daily. This may be a more likely medication choice for patients with a contraindication for naltrexone.
Abbreviations	**BID**: Twice a day, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD:** Methamphetamine use disorder, **N:** Number, **OD**: Once daily, **RCT**: Randomized controlled trial, **RoB:** Risk of Bias, **XL:** Extended-release
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings: AtStUD

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality)[ii]	Effect/Impact	Comments
Sustained stimulant abstinence	Critical	Moderate	Meta-analysis: Chan 2019[1] (Supplemental)	**No difference** between bupropion and placebo in continuous stimulant abstinence found in an earlier meta-analysis (Bhatt 2016)[2]. OR=1.12, 95% CI: 0.54-2.33, p=0.76. Three RCTs, n=361): • Anderson 2015 (12 wks 150 mg BID); Heinzerling 2014 (12 wks 150 mg BID); Shoptaw 2008 (MaUD, 12 wks 150 mg BID)	1 study was of CUD population

Stimulant abstinence (rate)	Critical	Moderate	Systematic review: Siefried 2020[3] (High)	**No difference** between bupropion and placebo in stimulant abstinence in the planned analyses.
				Bupropion favored compared to placebo in subgroups:
				• **baseline light (<18 using days/month) consumers:**
				  • Elkashef 2008 (12 wks, 150 mg BID); Shoptaw 2008 (MaUD, 12 wks, 150 mg BID)
				• **baseline light consumers who were medication adherent** as determined by plasma levels:
				  • Heinzerling 2014 (12 wks 150 mg BID)
				• **men:**
				  • Elkashef 2008 (12 wks, 150 mg BID)	

Stimulant use (rate)	Critical	Low	Systematic review: Lee 2018[4] (Moderate)	**Mixed evidence.** Of 7 studies (n=699), 3 studies and 1 secondary analysis showed benefit, and 3 studies showing no benefit: • Anderson 2015 (12 wks 150 mg BID); Das 2010 (XL 300 mg, 12 wks); Elkashef 2008 (12 wks, 150 mg BID); Heinzerling 2014 (12 wks 150 mg BID); Mooney 2016 (450 mg/day, 8 weeks); McCann & Li 2012 (150 mg BID); Shoptaw 2008 (MaUD, 12 wks 150 mg BID)	Some studies had low medication adherence.
			Systematic review: Siefried 2020[3] (High)	**No difference** in reduction in stimulant use between bupropion and placebo in planned analyses of 3 studies, n=361: • Anderson 2015 (12 wks 150 mg BID) • Heinzerling 2014 (12 wks 150 mg BID) • Shoptaw 2008 (MaUD, 12 wks 150 mg BID)	
Treatment retention	Critical	High	Meta-analysis: Chan 2019[1] (Supplemental)	**No difference** between bupropion and placebo in rate of dropout for any reason: RR= 1.02, 95% CI: 0.88-1.17, p=0.81. Five RCTs (n=542):	4 studies from (Bhatt 2016)[2] plus 1 new. 1

				• Das 2010 (12 wks, XL 300 mg); Shoptaw 2008 (MaUD, 12 wks 150 mg BID); Anderson 2015 (12 wks 150 mg BID); Elkashef 2008 (12 wks, 150 mg BID); Heinzerling 2014 (12 wks 150 mg BID)	study was of CUD
Adverse events	Important	Moderate	Meta-analysis: Chan 2019[1] (Supplemental)	**No dropouts due to severe adverse events** reported in 1 RCT • Elkashef 2008 (12 wks, 150 mg BID)	
			Systematic review: Lee 2018[4] (Moderate)	**No difference** in rate of adverse events in bupropion vs placebo in 7 studies of MaUD. Authors conclude that bupropion is safe and well tolerated. • Anderson 2015 (12 wks, 150 mg BID), Das 2010 (12 wks, XL 300 mg), Elkashef 2008 (12 wks, 150 mg BID); Heinzerling 2014 (12 wks 150 mg BID); McCann & Li 2012 (150 mg BID), Mooney 2016 (450 mg/day, 8 weeks); Shoptaw 2008 (MaUD, 12 wks, 150 mg BID)	Some studies had low medication adherence.
Other substance use reduction: Smoking	Important	High	Systematic review: Siefried 2020[3] (High)	**Greater reduction in cigarette smoking in bupropion + nicotine inhaler + counseling compared to counseling alone** found in 1 RCT of a mixed cocaine/meth use disorder population • Winhusen 2014 (CoUD/MaUD 10 wks 150-300 mg/d) Shoptaw 2008 (MaUD, 12 wks, 150 mg BID) also reported significantly reduced smoking compared to placebo, but the population was not explicitly described as having a nicotine use disorder.	Mixed cocaine/meth use disorder population

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Evidence to Decision Table: Bupropion for ATStUD

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Data from systematic review and meta-analysis suggest that bupropion is not effective for all individuals with ATS use disorder. However, in individuals with less-than-daily use and adherence with medication, evidence suggests that bupropion may reduce stimulant use. Additionally, data suggest bupropion may reduce comorbid cigarette smoking.	Evidence for efficacy is most suggestive for less than daily users. Dosing Medication adherence	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		

Evidence Summary	*Additional Considerations*	*Judgment*
No difference in rate of adverse events in bupropion vs placebo in 7 studies of MaUD.	In some studies, low rates of adverse events may have been related to poor medication adherence. Bupropion has been extensively studied for smoking cessation and other conditions like binge eating, and some adverse effects observed in these clinical trials are likely important to consider in the treatment of ATStUD. Bupropion should be avoided in individuals with history of seizure or eating disorders, and used with caution in individuals with elevated seizure risk.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence supports possible benefit of bupropion for ATS use disorder in people who use less than daily; no studies have demonstrated adverse effects in the treatment of ATStUD. Although both desirable and undesirable effects are small, the potential benefits outweigh the potential risks. Especially with the lack of strongly supported medication alternatives, the use of bupropion for ATStUD is supported.	Medication adherence.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence for efficacy is inconsistent across studies.		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
Outcomes not routinely examined that are of importance include quality of life, engaging in daily activities (eg, work), and reduction in other health outcomes (eg, HIV, hepatitis C, and STI acquisition).	No important uncertainty expected	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no

		☒ No ☐ Varies
*** Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Few minority population-specific data are available.		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Few data on acceptability available;	At face value, outcomes and potential efficacy are likely to be acceptable to most patients, clinicians, and policymakers. Bupropion is a commonly prescribed and generally well-tolerated medication. Bupropion is a generic medication and is commonly covered by insurance and savings clubs.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
*** Feasibility**: Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Bupropion is commonly used in a number of other conditions and is affordable. While relatively easy, dosing does require titration dosing. May not be feasible in treatment settings without staff with the ability to prescribe medication.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Especially in the context of the lack of strongly supported medication alternatives, the CGC agreed that bupropion may be considered as a pharmacotherapeutic option for amphetamine use disorder

Subgroup Considerations

Bupropion as a monotherapy treatment for ATSUD may be more effective with patients with a lower frequency use of ATS, which was defined in the trials as fewer 18 or fewer days/month of ATS use

Implementation Considerations

- Suggested dosing
- Bupropion should be avoided in patients with elevated seizure risk. (Approve 100%, Strong)

References

1. Chan B, Freeman M, Kondo K, et al. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. *Addiction*. 2019;114(12):2122-2136. doi:10/gn7632
2. Bhatt M, Zielinski L, Baker-Beal L, et al. Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a systematic review and meta-analysis. *Syst Rev*. 2016;5(1):189. doi:10.1186/s13643-016-0370-x
3. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
4. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018;191:309-337. doi:10.1016/j.drugalcdep.2018.06.038

Table 10. Bupropion + Naltrexone for Amphetamine-Type Stimulant Use Disorder

Recommendation: For patients with amphetamine-type StUD, clinicians can consider prescribing bupropion in combination with naltrexone to promote reduced use of amphetamine-type stimulants.

a. Clinicians can give this combination additional consideration for patients with a co-occurring alcohol use disorder, as naltrexone can also reduce alcohol consumption.
b. Clinicians should give this combination additional consideration for patients with a co-occurring tobacco use disorder, as naltrexone can also reduce nicotine/tobacco use.
c. Clinicians can give this combination additional consideration for patients with co occurring depressive disorders, as bupropion can also treat depression.

Clinical Question Summary Table

Clinical Question	1. Is the combination pharmacotherapy of bupropion and naltrexone safe and effective at reducing stimulant use and increasing treatment retention in patients with amphetamine-type stimulant use disorder? 2. What contextual factors and implementation strategies may influence the effects of bupropion + naltrexone?
Population	Patients with amphetamine-type stimulant use disorder
Intervention	Bupropion + Naltrexone
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, depressive symptoms, adverse events, opioid consumption, alcohol consumption, nicotine consumption
Setting	Inpatient or outpatient settings
Considerations	• Co-occurring opioid use disorder • Co-occurring alcohol use disorder • Co-occurring nicotine use disorder • Seizure risk (history of seizure, lower seizure threshold)
Background & Definitions	Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA-approved for the treatment of major depressive disorder (MDD), seasonal affective disorder, and smoking cessation Naltrexone is a mu opioid receptor antagonist that is FDA-approved for the treatment of AUD and OUD; its extended-release formulation is also approved for the prevention of OUD recurrence
Abbreviations	**ATStUD:** Amphetamine-type stimulant use disorder, **AUD:** Alcohol Use Disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N:** Number, **NUD**: Nicotine Use Disorder, **OD**: Once daily, **OUD**: Opioid Use Disorder, **RCT**: Randomized controlled trial, **RoB:** Risk of Bias, **UDS:** Urine drug screen, **UDT:** Urine drug test
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No systematic reviews or meta-analyses of bupropion + naltrexone for ATStUD were found.

Summary of Findings Table

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
End of treatment continuous abstinence	Critical	High	RCT: Trivedi 2021[1] (RoB High)	**Positive effect for Bupropion + Naltrexone:** More participants achieved continuous abstinence (≥75% MA-negative samples) in the last 2 weeks of treatment in the naltrexone-bupropion group compared to placebo (13.6% vs 2.5%, MD=11.1%, lower bound of 95% CI 6.3, p<0.001). • N=403 moderate or severe MaUD	≥3 MA-negative UDS out of 4 collected
			Pre-post: Mooney 2016[2] (Supplemental)	11 of 49 (24%) participants achieved continuous abstinence ≥75% MA-negative samples) during the last 4 weeks of treatment, significantly higher than the 9 participants needed to meet the study "success" criterion (p=0.0075). • N=49 severe MaUD	≥6 MA-negative UDS out of 8 collected
Serious adverse events	Critical	High	RCT: Trivedi 2021[1] (RoB High)	**No effect.** No significant difference between naltrexone-bupropion and placebo among participants with moderate or severe MaUD. SAEs occurred in 8 of 223 (3.6%) naltrexone–bupropion participants. • N=403 moderate or severe MaUD	
			Pre-post: Mooney 2016[2] (Supplemental)	Occurred in 2 (4.1%) participants. 1 SAE (a single generalized seizure) was related to bupropion. • N=49 severe MaUD	
Adverse events	Important	High	RCT: Trivedi 2021[1] (RoB High)	**No effect.** No significant difference between naltrexone-bupropion and placebo in overall rate of any adverse event (Stage 1: 91% vs 83%, p=0.08; Stage 2: 77% vs 69%, p=0.23). However, higher rate in naltrexone–bupropion group for some specific AEs (gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia). • N=403 moderate or severe MaUD	
			Pre-post: Mooney 2016[2] (Supplemental)	45 (92%) participants reported 249 adverse events during the study, 66.3% unrelated to study drugs. • N=49 severe MaUD	

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Individual Studies Table

Study (RoB*)	Design	Intervention(s)	Participants	Outcomes	Comments
Mooney 2016[2] (Supplemental)	Open-label pre-post Duration: 8 wks medication + 1 wk follow-up USA 3 sites (California, Hawaii, Texas)	Bupropion (Extended-release oral bupropion, Wellbutrin® XL 450 mg OD) and naltrexone (extended-release injectable naltrexone, Vivitrol 380mg) administered at weeks 1 and 5 Participants attended clinic twice weekly for observed bupropion dosing, UDS testing, assessments, and medical management. Other non-study treatment received not reported.	*Stage 1:* n=20 *Stage 2:* n=29 Treatment-seeking adults (age 18 to 65) with **severe MaUD** (DSM-5), self-reported ≥20 days of MA use in the 30 days prior to consent, and submitted 3 MA-positive UDS out of 4 collected during screening. 54% male, 49% white.	**Treatment response** (6 of 8 [75%] MA-negative UDS during the last four weeks of medication)**:** 11 of 49 participants responded to treatment, yielding response rate of 24% with 95% lower CI of 13%, higher than the "success" criterion of 9 responders, p=0.0075). Higher response rate (33%, 95% CI 17 to 53) in participants who were medication adherent. **Treatment-emergent adverse events (AEs):** 45/49 participants reported 249 AEs during the study, 66.3% unrelated to study drugs. **Serious adverse events (SAEs):** 2/49 participants experienced SAEs, 1 (a single generalized seizure) related to bupropion. **Medication adherence**: 86.6% of dispensed BRP doses taken as confirmed by dosing video or in-person observation. 80.6% participants with detectable hydroxybupropion blood levels (>1.00 ng/mL) at weeks 5 and 8. Naltrexone injection 1: 100%, injection 2: 83.7%. **Discontinued medication early:** 8/49 participants **Reduced medication dose:** 7/49 participants ***Responder vs non-responder analysis:*** **MA use (UDS-):** Proportion of MA-negative urines was significantly higher at each week for weeks 2–8 for the responder group as compared to the non-responder group (p=<0.05). **Craving** (VAS): Craving was significantly lower at each week for weeks 2–8 for the responder group as compared to the non-responder group (p=<0.05) **Quality of life** (Treatment Effectiveness Assessment; Ling, 2012): scores did not differ between responder and non-responder groups at baseline (p=0.54), but were significantly different at treatment end (p<0.001).	"Under the statistical analysis plan, study "success" required ≥ 9 responders. With 11 responders, the study demonstrated sufficient potential of naltrexone plus bupropion as a combination pharmacotherapy for MA use disorder to warrant further study." (p. 2)

Trivedi 2021[1] (RoB High)	RCT double-blind Sequential parallel comparison design (reduces % of placebo-responders) Duration: *Stage 1:* 6 wks + *Stage 2:* additional 6 wks for stage 1 placebo group non-responders USA Multi-site Outpatient	(1) Bupropion (extended-release 450 mg/day oral) + naltrexone (extended-release injectable 380 mg) every 3 weeks (2) Placebo All participants received weekly substance use counseling. Participants attended clinic twice weekly for UDS testing, assessments, and safety monitoring.	*Stage 1:* n=403 adults (age 18-65) with **moderate or severe MaUD** (DSM-5) not currently receiving SUD treatment, recruited through community advertising. Excluded if taking contraindicated medication or had increased risk of seizure. Inclusion of participants with co-occurring psychiatric disorder was evaluated on a case-by-case basis for a safety evaluation, but were not routinely excluded *Stage 2:* The 225 Stage 1 placebo group non-responders who were re-randomized for the additional 6 wks of Stage 2.	Intention-to-treat population includes randomized participants in stage 1 and rerandomized participants in stage 2. Results from both stages weighted and averaged for analysis**.** **Treatment response** (3 MA-negative UDS out of 4 obtained during the last 2 weeks of stage): More responders in the naltrexone-bupropion group compared to placebo (13.6% vs 2.5%, MD=11.1%, lower bound of 95% CI 6.3, p<0.001). **Any adverse event:** No sig difference in overall rate of AEs (Stage 1: 91% vs 83%, p=0.08; Stage 2: 77% vs 69%, p=0.23), but higher rate in naltrexone–bupropion group for some specific AEs (gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia). **Serious adverse events:** Occurred in 8 of 223 participants (3.6%) who received naltrexone–bupropion during the trial. In ITT sample, no sig difference between groups in rate of SAEs (Stage 1: 1/109 [0.9%) vs 4/294 [1.4%], p=1.00; Stage 2: 3/114 (2.6%) vs 4/111 (3.6%), p=0.72). **Medication adherence**: Stage 1: 75.1% in the naltrexone–bupropion group (63.9% to the oral regimen and 86.2% to the injection). Stage 2: 77.4% in the naltrexone–bupropion group (68.8% to the oral regimen and 86.4% to the injection)	Response rate was low, but higher than placebo. Favors combo for reduced MA use. Was there effect [of tx response] on total abstinence or sustained abstinence?

* RoB= Risk of Bias, assessed with the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

VAS: visual analogue scale of craving (values range from 0 to 100, with higher values indicating greater cravings);

PHQ-9: Patient Health Questionnaire 9; each of nine items is given a score of 0 to 3, with a score of 0 indicating the absence of depressive symptoms and a score of 3 indicating the presence of depressive symptoms nearly every day; total scores range from 0 to 27, with higher scores indicating greater depressive symptoms)

Treatment Effectiveness Assessment: assesses reduced substance use and improvements in lifestyle, health, and community and interpersonal interactions according to participant report24,25 (total scores range from 4 to 40, with higher scores indicating greater improvement in these factors).

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No systematic reviews or meta-analyses of bupropion + naltrexone XR for ATStUD were found. Evidence from one open-label trial and one RCT demonstrated reductions in MA	Studies enrolled participants with moderate or severe MaUD. The CGC viewed it as appropriate to extend the evidence to mild MaUD patients, although the effect may	☐ None ☐ Small ☒ Moderate

use (via urine drug screen) associated with this combination. The effect sizes for rate of BUP+XR-NTX participants achieving a period of continuous MA abstinence at the end of treatment were small, ranging from 13.6% to 24%. NNT of 8 or 9 for Trivedi	be smaller, and to other ATStUD populations because the pharmacotherapeutic mechanisms of effect are expected to be similar. However, the CGC did extend the results to CoUD despite BUP alone being recommended for patients with CoUD elsewhere in this guideline because Naltrexone is not expected to add additional benefit for this population. - In the RCT, XR-NTX dosing was every three weeks. The impact on undesirable effects of using a standard 4-week dosing regimen is unknown. Naltrexone is FDA approved for alcohol use disorder. Bupropion is FDA approved for smoking cessation. The combination of bupropion and naltrexone (as Contrave) is FDA approved for obesity.	☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Bupropion and naltrexone are generally well tolerated although some severe adverse events occurred in both studies.	- pain/injection site reactions possible with injectable medication - bupropion lowers seizure threshold	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Generally favors the intervention- weak evidence for efficacy, generally tolerable.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Limited number of studies, but large population. Judged to be low given the field for StUD as a whole. In the RCT, the mean difference in response rate (% participants achieving a period of MA abstinence in the last 4 weeks of treatment) between BUP+XR-NTX and Placebo was 11.1%, with a lower 95% CI boundary of 6.3%. In the open-label pre-post study, the response rate (% participants achieving a period of MA abstinence in the last 2 weeks of treatment) for BUP+XR-NTX was 24% with a lower 95% CI boundary of 13%,		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Possible uncertainty regarding side effects.	☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
*** Equity:** What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Potentially disparities in access to XR-NTX (more expensive), particularly given that the medication is not approved for this indication (so insurance authorization may be more difficult)	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability:** Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Likely variable acceptability --Initiation of XR-NTX requires opioid-free status -May have reluctance to take injectable formulation	☐ No ☐ Probably no ☐ Uncertain

		☐ Probably yes ☐ Yes ☒ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Requires prescriber technical skill, comfort with this combo requires capacity to administer injectable, confirmation of opioid-free status, coverage (pay) of injectable medication formulation If injection XR compared to oral naltrexone may be less important in this population compared to OUD. While oral formulation was not studied, … as oral formulations may be more feasible. May reduce adherence	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

While the evidence for bupropion alone is somewhat weak in patients with ATS use disorder, two recent studies using combination bupropion and naltrexone have shown more promise in terms of stimulant use outcomes

Subgroup Considerations

None noted

Implementation Considerations

- Clinicians might offer IM naltrexone q 3 weeks in combination with bupropion XL 450 mg/day.
- If acceptability or feasibility is affected by using an injectable formulation, consider oral naltrexone given that they are more feasible, may be more acceptable, and there is no evidence that oral formulation would be less effective.
- Bupropion should be avoided in patients with known seizure risk (eg, history or seizure, eating disorder). Refer to the manufacturer's label for other FDA contraindications.

Research Priorities

- Examine the utility of this combination in cocaine use disorder.

References

1. Mooney L, Hillhouse M, Thomas C, et al. Utilizing a two-stage design to investigate the safety and potential efficacy of monthly naltrexone plus once-daily bupropion as a treatment for methamphetamine use disorder. *J Addict Med*. 2016;10(4):236-243. doi:10/f8xf8x

2. Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *N Engl J Med*. 2021;384(2):140-153. doi:10.1056/NEJMoa2020214

Table 11. Topiramate for Amphetamine-Type Stimulant Use Disorder

Recommendation: For patients with amphetamine-type StUD, clinicians can consider prescribing topiramate to reduce use of ATS.

a. Clinicians can give topiramate additional consideration for patients with co-occurring alcohol use disorder, as this medication can also reduce alcohol consumption.

Clinical Question Summary Table

Clinical Question	Is topiramate safe and effective at reducing stimulant use and increasing treatment retention in patients with amphetamine-type stimulant use disorder?
Population	Patients with amphetamine-type stimulant use disorder
Intervention	Topiramate
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, adverse events, psychological symptoms, alcohol consumption
Setting	Inpatient or outpatient settings
Background & Definitions	Topiramate is an anticonvulsant medication that is FDA-approved for the treatment of epilepsy and migraine
Considerations	• Co-occurring alcohol use disorder • Co-occurring headaches
Abbreviations	**AUD:** Alcohol Use Disorder, **MA**: Methamphetamine, **N:** Number, **N/A**: Not applicable, **RCT:** Randomized Controlled Trial, **RoB:** Risk of Bias, **SR**: Systematic review, **ASI:** Addiction Severity Index, **UDS:** Urine Drug Screen, **TOP:** Topiramate, **AE:** Adverse events
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Sources (Quality)[ii]	Effect/Impact	Comments
Outcome Importance: Critical				
Global functioning	Moderate	2 Systematic reviews: Lee 2018[1] (Moderate); Siefried 2020[2] (High)	Both systematic reviews included the same 2 RCTs, which both found larger decreases in Addiction Severity Index (ASI) scores for topiramate vs placebo. • Elkashef 2012 (200 mg ID for 13 weeks) Clinical Global Impression Scale - Observer (CGI–O) score improved in topiramate arm compared to placebo (p=0.03).	

			• Rezaei 2016 (200 mg ID for 10 weeks).	
		Systematic review: Lee 2018[1] (Moderate)	Favors topiramate vs placebo in 1 RCT measuring Clinical Global Impression Scale - Observer (CGI–O) score improved in topiramate arm compared to placebo (p=0.03). • Elkashef 2012 (200 mg ID for 13 weeks)	
Stimulant use	Moderate	2 Systematic reviews: Lee 2018[1] (Moderate); Siefried 2020[2] (High)	Both systematic reviews included the same 2 RCTs, which both found greater reductions in methamphetamine use (measured by % negative UDS) for topiramate vs placebo. • Elkashef 2012 (200 mg ID for 13 weeks); Rezaei 2016 (200 mg ID for 10 weeks). Siefried 2020[2] also included Ma 2013, a re-analysis of Elkashef 2012	
Outcome Importance: Important				
Adverse events	Moderate	Systematic review: Lee 2018[1] (Moderate)	In 2 RCTs, no difference in rate of adverse events. One study had high dropout. • Elkashef 2012 (200 mg ID for 13 weeks); Rezaei 2016 (200 mg ID for 10 weeks).	

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence from two RCTs has demonstrated reduction in methamphetamine use via UDS associated with topiramate compared to placebo. Reductions in ASI scores were also demonstrated, suggesting improvements in addiction-related consequences and functioning.	-TOP also has evidence in treatment of alcohol use disorder so may be preferable in co-occurring AUD population. -Approved for treatment of migraines, seizure disorder.	☐ None ☒ Small ☐Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
One study showed higher dropout rates with TOP Generally similar rates of AEs across groups.	Topiramate has variable tolerability due to possible adverse effects: cognitive effects, paresthesias. Better tolerability if slow titration	☐ None ☒Small ☐ Moderate ☐ Large

		☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
Evidence, though weak generally favors use of topiramate.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence Summary	*Additional Considerations*	*Judgment*
Weak evidence favoring consumption outcomes.		☐ Clinical judgment (no evidence) ☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Research Evidence Summary	*Additional Considerations*	*Judgment*
No research evidence in this area	Possible uncertainty regarding side-effects.	☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
*** Equity:** What would be the impact on health inequities?		
Research Evidence	*Additional Considerations*	*Judgment*
Low-cost, generally available/accessible medication.	May reduce existing inequity in making medication more available to low income patients.	☐ Increased ☐ Probably increased ☐ Uncertain

	treatment would perhaps reduce health inequities if internists, primary care MDS used these meds, however, providers may be less familiar with use of TOP	☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability:** Is the option acceptable to key stakeholders?		
Research Evidence	*Additional Considerations*	*Judgment*
	Patients may have difficulty tolerating known adverse effects of the medication. Patient values may vary on willingness to take off-label medication with known potential side effects for MaUD.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence	*Additional Considerations*	*Judgment*
Generally feasible to implement in most settings, though titration schedule may be slow, and providers may have variable familiarity with the medication.	Need to address how widely available physicians who feel comfortable prescribing off-label medications, particularly the access to these physicians by URM groups. Some providers may be less familiar with use of TOP, titration.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

There is some evidence from RCTs for reduction in methamphetamine use, which is offset by tolerability concerns.

Subgroup Considerations

None noted

Implementation Considerations

The desirable effects of topiramate are somewhat offset by known side effects (eg, cognitive effects, paresthesia) and variable tolerability, which can be improved by slow titration

References

1. Lee N, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend.* 2018;191:309-337. https://doi.org/10/gfw5px
2. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x

Table 12. Mirtazapine for Amphetamine-Type Stimulant Use Disorder

Recommendation: For patients with amphetamine-type StUD, clinicians can consider prescribing mirtazapine to promote reduced use of amphetamine-type stimulants.

a. Clinicians can give mirtazapine additional consideration for patients with co-occurring depression, as this medication can also treat depression.

Clinical Question Summary Table

Clinical Question	Is mirtazapine a safe and effective treatment for amphetamine-type stimulant use disorder?
Population	Patients with amphetamine-type stimulant use disorder
Intervention	Mirtazapine
Comparison	Placebo
Main Outcomes	Stimulant use, treatment completion, depression and withdrawal symptoms, adverse events
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Notes • What do these medications do? • Why would we expect this treatment to benefit patients w/ StUD? • General dosing information/examples • An atypical antidepressant • "Mirtazapine has been shown to be safe and well tolerated (Nutt, 2002) and also appears to be useful in patients who have depression comorbid with anxiety symptoms and sleep disturbance (Anttila & Leinonen, 2001)." (McGregor 2008, p335)[1] • "Mirtazapine is an antidepressant with a relatively good tolerance and safety profile. It has been approved by the U.S. Food and Drug Administration and is commonly used to treat moderate to severe depression. Mirtazapine is a tetracyclic piperazinoazepine that enhances central noradrenergic and serotonergic activity by blocking alpha2 receptors and selectively antagonizing 5HT 2 and 5HT3 receptors (De Boer 1996). Mirtazapine has also shown to improve suicidal ideation, to show relatively few side effects, and to show little abuse potential." (Shoptaw 2009, p11)[2] • "Noradrenergic and specific serotonergic antidepressant. Mixed monoamine agonist/antagonistfacilitates release of norepinephrine, serotonin and dopamine in the CNS [87]" (Siefried 2020, p343)[3] •
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CES-D**: Center for Epidemiologic Studies Depression Scale, **CoUD**: Cocaine use disorder, **DASS**: Depression – Anxiety – Stress Scale, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, MDD: Major Depressive Disorder, **MD**: Mean difference, **MEMS**: medication event monitoring system **MSM**: Men who have sex with men, **N**: Number, **RCT**: Randomized Control Trial, **ROB**: Risk of Bias, **RR**: Risk ratio, **SMD**: Standard mean difference, **StUD**: Stimulant use disorder, **UDS**: Urine drug screen, **UDT**: Urine drug test
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Stimulant use	Critical	Moderate	Meta-analysis: Naji 2022[4] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo groups in MA use (%UDS+) @ 12 weeks in 2 high-quality RCTs conducted among cis-gender men, transgender men, and transgender women who have sex with men with MaUD (n=133, RR 0.81, 95% CI 0.63 to 1.03, p=0.09). Review author strength of evidence rating: Moderate due to imprecision "as the confidence interval includes both a small important reduction as well as no benefit" (p. 4). • Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d); Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d)	MaUD
			Meta-analysis: Chan 2019[5] (Supplemental)	**Positive effect for Mirtazapine. Mirtazapine > placebo**: Mirtazapine group had more negative UDSs, with a larger increase in the number negative UTS participants at trial end in 1 high risk of bias RCT of MSM with MaUD. Review author strength of evidence rating: Insufficient • Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d)	MaUD
			Systematic review: Siefried 2020[3] (High)	**Mixed evidence** for reduction in MA use. Both studies had low medication adherence. • Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d) Favors mirtazapine; Cruickshank 2008 (n=31 MA withdrawal, 2 wks 30 mg/d) No difference	ATStUD
Treatment retention	Critical	Low	Meta-analysis: Naji 2022[4] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo in in retention in treatment @ 12 weeks in 2 RCTs (n=180, RR 1.01, 95% CI 0.91 to 1.12, p=0.89; I-squared 0%, p=0.85). Review author strength of evidence rating: Moderate • Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d); Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d)	MaUD in MSM
			Meta-analysis: Shoptaw 2009[2] (Moderate)	**No effect.** No significant difference between mirtazapine and placebo in dropout for any reason in 2 RCTs (RR 0.98, 95% CI 0.49 to 1.97, p=0.96; I-squared=0%, p=0.77) • Cruickshank 2008 (n=31 MA withdrawal, 2 wks 30 mg/d); Kongsakon 2005 (n=20 ATS withdrawal, 2 wks 15–30 mg/d)	ATS withdrawal

			Meta-analysis: Chan 2019[5] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo in groups in retention in 1 high risk of bias RCT of MSM with MaUD. Review author strength of evidence rating: Insufficient • Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d)	MaUD in MSM
Depressive symptoms	Important	Low	Meta-analysis: Naji 2022[4] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo in reduced depression symptom severity as measured by the CES-D scale at 12 weeks in 2 RCTs (n=153, MD 0.45, 95% CI -2.88 to 3.78, p=0.79; I-squared=0%, p=0.61). Review author strength of evidence rating: Moderate Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d) • Colfax 2011 (n=60 MaUD in MSM, 12 wsk 30 mg/d)	MaUD in MSM
Withdrawal symptoms	Important	Low	Meta-analysis: Shoptaw 2009[2] (Moderate)	**No effect.** No significant difference between mirtazapine and placebo on DASS depression subscale at 35 days in 1 RCT (SMD 0.17, 95% CI -0.54 to 0.89, p=0.63) • Cruickshank 2008 (n=31 MA withdrawal, 2 wks 30 mg/d)	MA withdrawal
			Systematic review: Siefried 2020[3] (High)	**Mixed evidence** for reduction of ATS withdrawal symptoms in 2 RCTs • Cruickshank 2008 (n=31 MA withdrawal, 2 wks 30 mg/d) No difference; Kongsakon 2005 (n=20 ATS withdrawal, 2 wks 15–30 mg/d) Favors mirtazapine	ATS withdrawal
High risk sexual behavior	Important	Low	Meta-analysis: Naji 2022[4] (Supplemental)	**Mixed evidence** on reduction in number of self-reported sexual partners in 2 RCTs (n=180). Review author strength of evidence rating: Very low • Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d) No difference in the number of sexual partners in the prior 4 wks at 12 weeks, fewer in mirtazapine group compared to placebo at 24 wks; Colfax 2011 (n=60, MaUD in MSM 12 wks 30 mg/d) Fewer sexual partners in the prior 4 wks in mirtazapine group compared to placebo at 12 wks.	MaUD in MSM Outcome heterogeneity precluded meta-analysis
Serious adverse events	Critical	Low	Meta-analysis: Naji 2022[4] (Supplemental)	**No effect.** No serious adverse events linked to mirtazapine reported in 2 RCTs. • Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d); Colfax 2011 (n=60, MaUD in MSM 12 wks 30 mg/d)	MaUD in MSM
Adverse events	Important	Low	Meta-analysis: Naji 2022[4] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo in 2 RCTs. Side effects included drowsiness (30–43%), weight gain (7–10%), increased appetite (2–13%).	MaUD in MSM

				• Coffin 2020 (n=120 MaUD in MSM, 24 wks 30 mg/d); Colfax 2011 (n=60, MaUD in MSM 12 wks 30 mg/d)	
			Meta-analysis: Chan 2019[5] (Supplemental)	**No effect.** No significant difference between mirtazapine and placebo in dropouts due to adverse events in 1 high risk of bias RCT. Review author strength of evidence rating: Insufficient. • Colfax 2011 (n=60 MaUD in MSM, 12 wks 30 mg/d)	MaUD in MSM

i: Strength of evidence (SOE) categories: High = further research is very unlikely to change confidence on the estimate of effect. Moderate = further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study (RoB*)	Design	Intervention	Participants	Outcomes	Comments
Coffin 2020[6] (Unclear RoB)	RCT, double-blind 24 wk medication phase, 12 wk follow-up USA Outpatient	(1) Mirtazapine (30 mg/d) (2) Placebo	N=120 cisgender male (n=115) and transgender female (n=5) adults who have sex with men with MA use disorder (DSM-IV-TR) who had sex while using MA in the prior 6 months interest in reducing or stopping MA use recruited from the community (51% white). Excluded current major depression or any psychiatric condition precluding safe participation	**MA use rate** (UDT): In ITT analysis, rate of MA-positive UDT declined among mirtazapine vs placebo group • @ 12 weeks (RR=0.67; 95% CI, 0.51-0.87; p=0.003) • @ 24 weeks (RR=0.75; 95% CI, 0.56-1.00; p=0.05) • @ 36 weeks (RR=0.73; 95% CI, 0.57-0.96; p=0.02) **EOTA (%n)**: n.s.d. between groups in % of participants achieving end-of-study abstinence. **Retention**: n.s.d. between groups **Dependence severity** (SDS): n.s.d. between groups **Depression** (CES-D): • n.s.d. between groups at wk 12 (p=0.9). • Mirtazapine had net reductions in depressive symptoms at wk 24 (MD= -6.2; 95% CI 1.3-11.1, p=0.01) • n.s.d. between groups at wk 36 (p=0.6). **Sleep** (AIS): • n.s.d. between groups at wk 12 (p=0.06). • Mirtazapine had net reductions in insomnia severity score at wk 24 (MD= -1.4; 95% CI, 0.1-2.7; p=0.04), • n.s.d. between groups at wk 36 (p=0.4) **Craving**: n.s.d. between groups	In Siefried 2020[3] and Naji 2022[4]: Low risk of bias Low adherence: Participants taking at least 50% of their study medications at week 12 (37% vs 35%) and week 24 (22% vs 20%).

				Sexual risk behaviors: n.s.d between groups in reported number of sexual partners in past 4 weeks at baseline compared to 12-weeks (n=0.97). Mirtazapine group had fewer partners at 24 wks (RR=0.52; 95% CI, 0.27-0.97); p=0.04). Same time pattern for episodes of condomless anal sex with partners who were serodiscordant and episodes of condomless receptive anal sex with partners who were serodiscordant.	
Colfax 2011[7] (Supplemental)	RCT, double-blind 12 wks USA Outpatient	(1) Mirtazapine (30 mg/d) (2) Placebo All participants received 30-minutes/week CBT/MI substance use counseling. UTS 1x/wk	N=60 cisgender adult (age 18-60) sexually active MSM with MA dependence (DSM-IV-TR) recruited at STD and HIV clinics, bars, and community-based organizations (62% White). Excluded major depressive disorder.	**Retention:** NSD between groups (28/30, 93% vs 28/30, 93%) **Change in stimulant use rate (UDS+):** Risk of MA-pos UDS decreased faster in the mirtazapine group compared to placebo (RR 0.57, 95% CI 0.35-0.93, p=0.02). Greater decrease in rate of MA-pos UDS from baseline to week 12 in mirtazapine group compared to placebo (MD -40% vs -6%). Number needed to treat to achieve a negative weekly urine test result was 3.1 **Depression** (CES-D): NSD between groups; overall decrease over time. But, excluded participants with MDD. **Sexual risk behaviors:** Risk behaviors decreased faster in the mirtazapine group compared with placebo in most sexual risk behaviors analyzed: n male partners (RR= 0.20, 95%CI 0.04-0.93, p=0.04), anal sex with serodiscordant partners, unprotected anal sex with serodiscordant partners, insertive unprotected anal sex with serodiscordant partners. Number of male partners decreased in mirtazapine group, but increased in placebo group by week 12 (MD= -8.5 vs 15.5,) **Adverse events:** n.s.d in rate of AE between groups; most were mild to moderate. Most common: increased alanine aminotransferase levels (9 [23%] vs 7 [30%]), increased aspartate aminotransferase levels (5 [17%] vs 8 [27%]), gastroenteritis (4 [13%] vs 4 [13%]), upper respiratory tract infection (3 [10%] vs 4 [13%]), hyperglycemia (4 [13%] vs 3 [10%]). Expected adverse effects reported exclusively in the mirtazapine arm included drowsiness (13 participants [43%]), increased appetite (4 [13%]), and weight gain (3 [10%]). **Serious adverse events**: No serious adverse events related to study drug were reported. 2 SAEs occurred; Mirtazapine: MA-induced paranoia n=1 (3%), Placebo: vertebral fracture n=1 (3%)	In Siefried 2020[3]; Chan 2019[5]: RoB unclear; Naji 2022[4]: Low risk of bias ITT analysis using generalized estimating equations model Low to moderate adherence: Adherence by MEMS was 48.5% (48.3% for mirtazapine, 48.7% for placebo). Self-report adherence was 74.7% (75.9% for mirtazapine, 73.5% for placebo).
Cruickshank 2008[8] (Supplemental)	RCT, double-blind	(1) Mirtazapine (15 mg/d for 2 days, 30 mg/d for 12 days)	N=31 amphetamine or MA-dependent (DSM-IV) adults (age	**Retention**: n.s.d. between groups @ day 14 (7/13 vs 9/18) or @ day 35 (4/13 vs 6/18).	In Siefried 2020[3] and Shoptaw 2009[2]

	2 wk medication phase 35-day follow-up Australia Outpatient	(2) Placebo All participants were offered narrative therapy counselling	18-65) who used amphetamines in the 72 hours prior to recruitment experiencing withdrawal (63% men). 66% of participants scored above the ACSA cutoff indicating non-organic insomnia.	**Time in treatment**: n.s.d. between groups (18 vs 16 days, t(29)=70.484, p<0.05) **MA use** (OTI-Quantity subscale): n.s.d between groups @ either time; improvement in both groups @ day 14. **Dependence** (SDS)**:** n.s.d between groups @ either time or over time @ day 14 **Depression** (DASS subscale): n.s.d between groups @ either time **Anxiety** (DASS subscale): n.s.d between groups @ either time. However, significantly higher baseline anxiety score in mirtazapine group compared to placebo (mean 23 vs 18, p<0.05). **Stress** (DASS subscale): Trend for lower score @ day 14 in mirtazapine group (18.6 vs 24.5, p=0.057). n.s.d between groups @ day 35. **Withdrawal symptoms** (ACSA): n.s.d between groups @ any time; improvement in both groups. **Psychiatric morbidity** (BSI-GSI): n.s.d between groups @ either time; improvement in both groups. **Sleep** (AIS-5): Mixed evidence. At baseline, more hours slept previous night (8 vs 5, p=0.043) in mirtazapine group compared to placebo. • Higher nocturnal awakening item score among the mirtazapine group compared to placebo @ day 14 (2.0 vs 0.9, p=0.041). • n.s.d. between groups in overall score @ day 14 (8 vs 3.8, p=0.09); improvement in both groups. • n.s.d. between groups @ 35 days	ITT analysis Better baseline sleep but higher baseline anxiety in mirtazapine group compared to placebo
Kongsakon 2005[9] (Supplemental)	RCT, unblinded 14 days Thailand Controlled setting (correctional facility)	(1) Mirtazapine (15–30 mg/d) (2) Placebo No additional psychotherapy	N=20 amphetamine dependence (DSM-IV)	**Retention**: 7/9 vs 9/11 **Withdrawal severity** (AWQ): Greater reduction in mirtazapine group compared to placebo at days 3 (p<0.005) and 14 (p<0.030). **Depression** (MADRS): No significant difference or decrease over time, **Adverse events**: Mild adverse events, such as headache, sedation, nausea and vomiting, were reported.	In Siefried 2020[3] and Shoptaw 2009[2]
McGregor 2008[1] (Supplemental)	Historical cohort study, open-label	(1) Mirtazapine (60 mg/d, PM dosing) (2) Modafinil (400 mg/d, AM dosing)	N=49 adults (age 18-65) admitted for MA withdrawal (DSM-IV TR) treatment who	**Withdrawal severity** (ACSA, 0-64): Mean score over 10 days • Modafinil > TAU (29.7 vs 40.9, p=0.001) • Mirtazapine > TAU (33.7 vs 40.9, p=0.001)	In Perez-Mana 2013[10]

	Data collected Aug 2003-Nov 2004 Duration typically 10 days Australia Inpatient	(3) TAU (as needed antipsychotic Pericyazine 2.5–10 mg) group did not provide information on drug effects or sleep patterns Symptomatic medications were available as-needed (diazepam, nitrazepam, temazepam).	used amphetamines within the previous 96 hours. Excluded other SUD except nicotine.	• Modafinil > Mirtazapine (29.7 vs 33.7, p=0.041) over first 7 days, then no sig diff. **Withdrawal symptoms** (ACSA items, 0-4): Mean score over 10 days • Modafinil > TAU in fatigue (p<0.001), agitation (p<0.001), anxiety (p<0.001), irritability (p<0.001), anhedonia (p = .005), vivid dreams (p<0.001), suicidal ideation (p<0.001), inactivity (p = .042), tension (p<0.001), hypersomnia (p<0.001), and craving frequency (p = .012) • Mirtazapine > TAU in fatigue (p = .035), agitation (p = .014), anxiety (p = .018), irritability (p = .022), paranoid ideation (p<0.001), anhedonia (p< 0.001), vivid dreams (p = 0.006), and suicidal ideation (p<0.001) • Modafinil > Mirtazapine in fatigue (p<0.001), agitation (p=0.028), anxiety (p=0.008), irritability (p=0.005), tension (p=0.033), and craving frequency (p=0.012) **Global state** (CGI-O, 0-7): Modafinil > TAU (2.4 vs 3.1, p=0.001), Modafinil > Mirtazapine (2.4 vs 2.9, 0.014). No sig diff between Mirtazapine and TAU. **Sleep** (St. Mary's Hospital Sleep Questionnaire): Modafinil group had deeper sleep compared to mirtazapine (p=0.019) and fewer nighttime awakenings (1.7 vs 2.4, p=0.01). The Mirtazapine group reported significantly more hours asleep during the day (p=0.012), at night (p=0.015), and in total (p=0.002) compared to the modafinil group. Significant interaction in sleep quality (p=0.013). Effects not explained by authors. In figure, appears Modafinil group had poorer sleep quality at baseline compared to Mirtazapine. Quality improved over time in Modafinil group but declined over time in Mirtazapine group. **Serious adverse events:** None reported	

* RoB= Risk of Bias, assessed with the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
ACSA = Amphetamine Cessation Symptoms Assessment
AIS-5 = 5-item Athens Insomnia Scale
BSI = Brief Symptom Inventory
BSI-GSI= Brief Symptom Inventory (BSI) subscale
CES-D = Center for Epidemiologic Studies Depression Scale
DASS = Depression – Anxiety – Stress Scale

HAM-D = Hamilton Depression Scale
OTI = Opiate Treatment Index
MADRS = Montgomery–Åsberg Depression Rating Scale
SDS = Severity of Dependence scale

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Holmwood C, Gowing L. *Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults*. Clinical Guideline No. CG284. Drug and Alcohol Services South Australia (DASSA); 2019. https://www.sahealth.sa.gov.au/wps/wcm/connect/Public%20Content/SA%20Health%20Internet/Resources/Policies/Acute%20Presentations%20Related%20to%20Methamphetamine%20Use%20Clinical%20Guideline

Manning V, Arunogiri S, Frei M, et al. *Alcohol and Other Drug Withdrawal: Practice Guidelines*. 3rd ed. Turning Point; 2018.

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.

Non-Systematic Reviews & Commentary

Source		Comments
Chakravorty 2018[11]	**Cocaine and its associated sleep disorders** • Medications with demonstrated efficacy in improving sleep continuity disturbance in individuals with cocaine use disorder: Modafinil, lorazepam, tiagabine and mirtazapine • Mirtazapine improved sleep onset latency in depressed subjects with CoUD after 4 weeks [38].	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Two randomized, placebo-controlled trials showed a small benefit of Mirtazapine 30 mg/d in reducing ATS use among MSM with ATStUD compared to placebo (Coffin 2020[6]; Colfax 2011[7]). Colfax 2011[7] reported the number needed to treat to achieve a negative weekly urine test result was 3.1. Both studies also reported a significant reduction in sexual risk behaviors in patients treated with Mirtazapine compared to placebo.	MSM may value reduction in sexual risk behavior more than other patients The CGC felt it is appropriate to extend these results to heterosexual men and to women.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know

Mirtazapine also had a positive effect on sleep. Both studies were conducted with MSM.		
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No significant difference in rate of adverse events between groups treated with mirtazapine and placebo in 2 RCTs of MSM with MaUD (Coffin 2020[6]; Colfax 2011[7]). Side effects included drowsiness (30–43%), weight gain (7–10%), increased appetite (2–13%). No serious adverse events linked to mirtazapine reported in 2 RCTs of MSM with MaUD (Coffin 2020[6]; Colfax 2011[7]).		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	While evidence is weak, because there are few medication options available, the CGC determined that mirtazapine that preferable to no treatment at all.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Two RCTs showed a benefit in reducing ATS use compared to placebo.	Although there are only 2 studies, the CGC considered this of low strength in the context of research for effective medications to treat ATStUD.	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*

	Possible uncertainty around value/preference for avoidance of adverse effects such as weight gain, drowsiness	☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Mirtazapine is widely available, although using it for this indication will likely depend on specialist care. Inequity could be increased or decreased depending on implementation.	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Mirtazapine is widely available and easy to provide. It may also help with depression, anxiety.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Mirtazapine is widely available and easy to provide. Is FDA approved with no abuse liability.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusions

Justification

While meta-analyses and systematic reviews largely reported mixed or no evidence for mirtazapine, two randomized placebo-controlled trials showed a small reduction in ATS use

Subgroup Considerations

Studies were conducted in MSM however appropriate to apply more generally

Implementation Considerations

- Check for medication interactions
- Patient concern about weight gain
- Useful for anxiety (calming effect)
- Indication for co-occurring MDD

Research Priorities

- Mirtazapine should be tested in other populations of methamphetamine users.

References

1. McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: A comparison of mirtazapine and modafinil with treatment as usual. *J Subst Use Addict Treat*. 2008;35(3):334-342. doi:10.1016/j.jsat.2007.12.003
2. Shoptaw SJ, Kao U, Heinzerling K, Ling W. Treatment for amphetamine withdrawal. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online April 15, 2009. doi:10.1002/14651858.CD003021.pub2
3. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
4. Naji L, Dennis B, Rosic T, et al. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. *Drug Alcohol Depend*. 2022;232:109295. doi:10.1016/j.drugalcdep.2022.109295
5. Chan B, Freeman M, Kondo K, et al. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. *Addiction*. 2019;114(12):2122-2136. doi:10/gn7632
6. Coffin P, Santos G, Ahmadi J, et al. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA psychiatry*. 2020;77(3):246-255. doi:10.1001/jamapsychiatry.2019.3655
7. Colfax GN, Santos GM, Das M, et al. Mirtazapine to reduce methamphetamine use: A randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(11):1168-1175. doi:10.1001/archgenpsychiatry.2011.124
8. Cruickshank CC, Montebello ME, Dyer KR, et al. A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev*. 2008;27(3):326-333. doi:10.1080/09595230801935672
9. Kongsakon R, Papadopoulos KI, Saguansiritham R. Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *Int Clin Psychopharmacol*. 2005;20(5):253-256. doi:10.1097/01.yic.0000166815.83017.d8

10. Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 2, 2013. doi:10/gn757q
11. Chakravorty S, Vandrey RG, He S, Stein MD. Sleep Management Among Patients with Substance Use Disorders. *Med Clin North Am*. 2018;102(4):733-743. doi:10.1016/j.mcna.2018.02.012

Table 13. Modafinil for Cocaine Use Disorder

Recommendation: For patients with cocaine use disorder and without a co-occurring alcohol use disorder, clinicians can consider prescribing modafinil to reduce cocaine use and improve treatment retention.

Clinical Question Summary Table

Clinical Question	Is modafinil a safe and effective treatment for patients with cocaine use disorder?
Population	Patients with cocaine use disorder
Intervention	Modafinil
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, adverse events, ADHD symptoms
Setting	Inpatient or outpatient specialty SUD treatment
Considerations	Co-occurring ADHD Co-occurring AUD
Background & Definitions	Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy. Narcolepsy is caused by dysfunction of a family of wakefulness-promoting and sleep-suppressing peptides, the orexins, whose neurons are activated by modafinil. The prexin neuron activation is associated with psychoactivation and euphoria. The exact mechanism of action is unclear, although in vitro studies have shown it to inhibit the reuptake of dopamine by binding to the dopamine reuptake pump, and lead to an increase in extracellular dopamine. Modafinil activates glutamatergic circuits while inhibiting GABA. For patients experiencing cocaine use disorder, clinicians might consider prescribing Modafinil 200mg or 400mg PO QD to get more non-use days for these patients. Notes • Modafinil inhibits metabolism of steroidal contraceptives via CYP3A4 and can reduce the effectiveness of this type of birth control, female subjects must use one of the following methods of birth control: barrier methods (diaphragm or condoms with spermicide or both), surgical sterilization, use of an intra-uterine contraceptive device, or complete abstinence from sexual intercourse. (See 2018)[1] • Brand name Provigil • What do these medications do? • Why would we expect this treatment to benefit patients w/ StUD? • General dosing information/examples
Abbreviations	**ADHD:** Attention Deficit Hyperactivity Disorder, **AUD**: Alcohol use disorder, **AWS**: Alcohol Withdrawal Syndrome, **BE:** benzoylecgonine, **GABA:** Gamma aminobutyric acid, **MA**: Methamphetamine, **N**: Number, **OD**: Once daily, **RCT**: Randomized Controlled Trial, **RD:** Risk deviation, **RoB:** Risk of Bias, **RR:** Risk ratio, **SMD:** Standard mean deviation, **UDT**: Urine drug test

Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments	Individual Studies Included
Continuous stimulant abstinence	Critical	Moderate	Meta-analysis: Tardelli 2020[2] (Moderate)	**No effect.** No significant difference between Modafinil and Placebo in likelihood of 2–3 weeks of sustained abstinence (8 RCTs, 970 participants, Risk Ratio [RR] 1.22, 95% CI 0.83-1.77, p=0.31). All studies conducted in outpatient settings.	Many studies had low medication adherence. • Studies were of MaUD patients. 1 study used combination modafinil + dexamphetamine	Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg); Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg); Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Schmitz 2012 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg + dexamphetamine 50 mg); Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg); Anderson 2012 (n=210 MaUD & no other SUD ex. nicotine/cannabis, 12 wks 200 mg OD or 400 mg OD); Heinzerling 2010 (n=71 MaUD & no alcohol, cocaine, opiate, benzo use disorder, 12 wks 400 mg OD)
			Meta-analysis: Castells 2016[3] (Supplemental)	**No effect.** No significant difference between Modafinil and Placebo in number of patients who achieved sustained cocaine abstinence regardless of definition used for the length of abstinence (6 RCTs, 644 participants, 25% vs 19%, RR 1.32, 95% CI 0.85-2.04, p=0.22). All studies	Many studies had low medication adherence. 1 study used combination modafinil + dexamphetamine	Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg); Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg); Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Schmitz 2012 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg + dexamphetamine 50 mg); Schmitz 2014

				conducted in outpatient settings.		(n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg)
Stimulant abstinence rate (%n)	Critical	Low	Meta-analysis: Sangroula 2017[4] (Low)	**No effect.** No significant difference between Modafinil and Placebo in the proportion of participants who were cocaine abstinent by urine BE or self-report (7 RCTs, 9 comparisons, 696 participants, RR 1.26, 95% CI 0.81-1.95, p=0.302; I^2=35.7%, p=0.133). The Egger test (intercept = 1.259, 95% CI = 0.813–1.949, p=0.302) did not indicate the presence of publication bias. <u>Subgroup analysis:</u> **Positive effect for Modafinil.** **Modafinil > placebo** for cocaine abstinence rate for the 6 RCTs conducted in the United States (8 comparisons, 669 participants, RR 1.44, 95% CI 1.03–2.02, p=0.035). **Negative effect for Modafinil. Placebo > modafinil** for cocaine abstinence rate in the 1 non-US study (27 participants: RR 0.103, 95% CI 0.015–0.706, p=0.021).	1 study used combination modafinil + dexamphetamine	<u>Subgroup analysis:</u> United States studies Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg); Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg); Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Morgan 2016 (n=57 CoUD & no other SUD ex. nicotine, 6 wks 100-400 mg) ; Schmitz 2012 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg + dexamphetamine 50 mg) Non-US studies Karila 2016 (n=27 men w CoUD France, 12 wks 200-400 mg) <u>Meta-regression analysis:</u> Included studies not listed

				Meta-regression analysis: Superiority of modafinil to placebo in abstinence rate was associated with **higher frequency of cocaine use at trial start** (8 studies, 639 participants, coefficient= –0.653, 95% CI -1.252 to -0.054, p=0.033)		
Stimulant abstinence rate (%UDT)	Critical	N/A	Meta-analysis: Sangroula 2017[4] (Low)	**Positive effect for Modafinil. Modafinil > placebo** in the number of BE-negative UDT samples throughout the trial (4 RCTs, 257 participants, SMD = -0.633, 95% CI -1.248 to 0.018, p=0.044), but significant heterogeneity between studies (p=0.001).	Authors did not identify the set of studies included in analyses	Included studies not listed
			Meta-analysis: Castells 2016[3] (Supplemental)	**Positive effect for Modafinil. Modafinil > placebo** in mean proportion of BE-negative UDT across the study per participant (1 RCT, n=57, 52 vs 26, SMD=0.59, 95% CI 0.06-1.12, p=0.03).		Morgan 2016 (n=57 CoUD & no other SUD ex. nicotine, 6 wks 100-400 mg)
Stimulant abstinence days	Critical	N/A	Meta-analysis: Sangroula 2017[4] (Low)	**Positive effect for Modafinil. Modafinil > placebo** in number of cocaine non-use day (3 studies, 267 participants, SMD = -1.294, 95% CI -2.572 to 0.017,	Authors did not identify the set of studies included in analyses	Included studies not listed

				p=0.047), but significant heterogeneity between studies (p<0.001).		
Treatment retention	Critical	Moderate	Meta-analysis: Sangroula 2017[4] (Low)	**No effect.** No significant difference between Modafinil and Placebo in treatment retention rate in the planned analysis (11 studies, 891 participants, RR 1.03, 95% CI 0.918-1.156, p=0.613; I^2=37.1%, p=0.087). The Egger test (intercept = 1.030, 95% CI 0.918–1.156, p=0.613) did not indicate the presence of publication bias <u>Meta-regression analysis:</u> The superiority of modafinil to placebo treatment retention was associated with **higher percent of male participants** (11 studies, 776 participants, coefficient= -0.023, 95% CI -0.039 to -0.007, p=0.005).	1 study used combination modafinil + dexamphetamine Kampman 2015b = Kampman 2018[5], NCT00368290 McRae-Clark 2016 = See 2018[1], NCT00613015	Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg); Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg); Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Kampman 2018 NCT00368290 (n=70 CoUD & no other SUD ex. nicotine, 8 wks 300 mg); Karila 2016 (n=27 men w CoUD France, 12 wks 200-400 mg); McRae-Clark 2018 NCT00613015 (n=59 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 3 days dose not reported); Morgan 2010 (n=20 CoUD & no other SUD ex. nicotine, 16 days 100-400 mg); Morgan 2016 (n=57 CoUD & no other SUD ex. nicotine, 6 wks 100-400 mg) ; Schmitz 2012 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg + dexamphetamine 50 mg)
			Meta-analysis: Castells 2016[3] (Supplemental)	**No effect.** No significant difference between Modafinil and Placebo in completion rate (7 RCTs, 723 participants, 60% vs 58%, RR 1.04, 95% CI 0.89-1.21, p=0.62).	1 study used combination modafinil + dexamphetamine	Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg); Dackis 2005 (n=62 CoUD & no other SUD ex. - nicotine, 8 wks 400 mg); Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Kampman 2018 NCT00368290 (n=70 CoUD & no other

						SUD ex. nicotine, 8 wks 300 mg); Schmitz 2012 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg + dexamphetamine 50 mg); Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg)
Serious adverse events	Critical	Moderate	Meta-analysis: Sangroula 2017[4] (Low)	**No effect.** No significant difference between Modafinil and Placebo in number of serious adverse events. Modafinil was not associated with increased number of serious adverse effects compared to placebo (5 studies, 265 participants, RR 0.765, 95% CI 0.42-1.40, p=0.39).	Authors did not identify the set of studies included in analyses	Included studies not listed
			Meta-analysis: Castells 2016[3] (Supplemental)	**No effect.** No significant difference between Modafinil and Placebo in number of patients experiencing serious adverse events (4 studies, 275 participants, 13/136 [9.6%] vs 21/139 [15.1%], Risk Difference = -0.02, 95% CI -0.08 to 0.04, p=0.48).		Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg); Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg); Kampman 2020 NCT00142818 (n=79 CoUD & AUD, 13 wks 400 mg/d) n=17; Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg) n=2
Adverse events	Important	N/A	Meta-analysis: Sangroula 2017[4] (Low)	**No effect.** No significant difference between Modafinil and Placebo in number of participants experiencing at least one adverse event (3 studies, 230 participants, RR	Authors did not identify the set of studies included in analyses	Included studies not listed

				1.194, 95%CI 0.383-3.722, p=0.76).		
Dropouts due to adverse events	Important		Meta-analysis: Castells 2016[3] (Supplemental)	**No effect.** No significant difference between Modafinil and Placebo in dropouts due to adverse events (4 RCTs, n=406, 12/237 [5.1%] vs 9/169 [5.3%], p=0.46).		Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg) n=17/207; Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg) n=0/62; Kampman 2015 (n=94 CoUD & no other SUD ex. -nicotine/cannabis, 8 wks 300 mg) n=2/94; Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg) n=2/36
Dropouts due to cardiovascular adverse events	Important	Low	Meta-analysis: Castells 2016[3] (Supplemental)	**No effect.** No significant difference between Modafinil and Placebo in dropouts due to cardiovascular adverse events (1 RCT, n=40, 0/22 [0.0%] vs 1/18 [5.5%], p=0.42)		Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg)
Discontinuation due to side effects	Important	N/A	Meta-analysis: Sangroula 2017[4] (Low)	**No effect.** No significant difference between Modafinil and Placebo (3 studies, 246 participants, RR 0.829, 95% CI 0.204-3.374, p=0.793)	Authors did not identify the set of studies included in analyses	Included studies not listed

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

>: Superior to

Studies which excluded patients with alcohol use disorder:

- Dackis 2005 (n=62 CoUD & no other SUD ex. nicotine, 8 wks 400 mg)
- Dackis 2012 (n=210 CoUD & no other SUD ex. nicotine, 8 wks 200 mg or 400 mg)
- Kampman 2015 (n=94 CoUD & no other SUD ex. nicotine/cannabis, 8 wks 300 mg)
- Kampman 2018 NCT00368290 (n=70 CoUD & no other SUD ex. nicotine, 8 wks 300 mg)
- Morgan 2010 (n=20 CoUD & no other SUD ex. nicotine, 16 days 100-400 mg)

- Morgan 2016 (n=57 CoUD & no other SUD ex. nicotine, 6 wks 100-400 mg)
- Schmitz 2014 (n=36 CoUD & no other SUD ex. nicotine/cannabis, 12 wks 200-400 mg)

Studies which included patients with alcohol use disorder:

- Anderson 2009 (n=207 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 12 wks 200 mg or 400 mg)
- McRae-Clark 2018 NCT00613015 (n=59 CoUD & no other SUD ex. alcohol/nicotine/cannabis & no AWS, 3 days dose not reported)
- Kampman 2020 NCT00142818 (n=79 CoUD & AUD, 13 wks 400 mg/d) n=17
- Karila 2016 (n=27 men w CoUD France, 12 wks 200-400 mg)

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
For cocaine use disorder patient, more non-use days with either dosage (200 mg/day or 400 mg/day) of modafinil compared to placebo There is mixed evidence for the effectiveness of modafinil in reducing stimulant use in CoUD patients. Two meta-analyses found no effect on sustained cocaine abstinence, but a positive effect on cocaine abstinence rates overall in patients treated with modafinil (Castells 2016[3]; Sangroula 2017[4]). Modafinil has shown efficacy in certain subpopulations, namely those without comorbid alcohol use disorder and those with high adherence to treatment.	Stronger evidence in populations without co-occurring alcohol use disorder Different results in studies that include/exclude patients with co-occurring AUD.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Modafinil is generally well tolerated. There were no significant differences in the rate of serious adverse events in 2 meta-analyses. Castells 2016[3] reported [low/moderate/high/acceptable] rates of serious adverse events (13/136, 9.6%), dropouts due to any adverse events (12/237, 5.1%), and dropouts due to cardiovascular adverse events (1/18, 5.5%) in patients assigned to modafinil conditions.		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither

		☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	For patients without co-occurring AUD	☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
*** Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Medication may be expensive and not covered by insurance if prescribed off-label	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No difference between modafinil and placebo groups in number of adverse events		☐ No ☐ Probably no ☐ Uncertain

		☒ Probably yes ☐ Yes ☐ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Generally feasible No special training required to prescribe	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

The evidence is mixed regarding the effectiveness of modafinil in reducing cocaine use in patients with cocaine use disorder

Subgroup Considerations

No relevant literature was identified regarding clinical effectiveness of modafinil for the treatment of patients with co-occurring cocaine use disorder and ADHD; therefore, no conclusions regarding the use of modafinil for these patients were made. While modafinil is used to treat ADHD, it is not currently FDA approved for this purpose.

Modafinil may be particularly beneficial for patients with higher frequency of cocaine use at treatment start.

Implementation Considerations

Medication adherence may be an issue

References

1. See RE. Stress and medication effects on cocaine cue reactivity. NCT00613015. Updated June 4, 2018. https://clinicaltrials.gov/study/NCT0061301
2. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2020;237(8):2233-2255. doi:10.1007/s00213-020-05563-3
3. Castells X, Cunill R, Pérez-Mañá C, Vidal X, Capellà D. Psychostimulant drugs for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 27, 2016. doi:10.1002/14651858.CD007380.pub4
4. Sangroula D, Motiwala F, Wagle B, Shah VC, Hagi K, Lippmann S. Modafinil Treatment of Cocaine Dependence: A Systematic Review and Meta-Analysis. *Substance Use Misuse*. 2017;52(10):1292-1306. doi:10.1080/10826084.2016.1276597
5. Kampman KM. Modafinil Treatment for Cocaine Dependence and HIV-High Risk Behavior. Updated March 15, 2018. https://clinicaltrials.gov/study/NCT00368290

Table 14. Topiramate + Extended-Release Mixed Amphetamine Salts for Cocaine Use Disorder

Recommendation: For patients with cocaine use disorder, clinicians can consider prescribing a combination of topiramate and extended-release mixed amphetamine salts to reduce cocaine use and cocaine craving.

a. Clinicians can give this combination additional consideration for patients with co-occurring alcohol use disorder, as topiramate can also reduce alcohol use.
b. Clinicians can give this combination additional consideration for patients with co-occurring ADHD, as MAS-ER can also reduce ADHD symptoms.

Clinical Question Summary Table

Clinical Question	1. Is the combination pharmacotherapy of extended-release mixed amphetamine salts (MAS-ER) and topiramate safe and effective treatment for patients with cocaine use disorder? 2. What contextual factors and implementation strategies may influence the effects of MAS-ER+Topiramate?
Population	Patients with cocaine use disorder
Intervention	Extended-release mixed amphetamine salts + Topiramate
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, adverse events, psychological symptoms, ADHD symptoms, alcohol consumption
Setting	Inpatient or outpatient settings
Considerations	• Co-occurring alcohol use disorder • History of seizure/lower seizure threshold (prefer to bupropion)
Background & Definitions	Notes • What do these medications do? • Why would we expect this treatment to benefit patients w/ StUD? • General dosing information/examples
Abbreviations	**ADHD:** Attention Deficit Hyperactivity Disorder, **AUD:** Alcohol use disorder, **CI:** Confidence Interval, **CM**: Contingency Management, **ERMS-AMP**: extended-release mixed amphetamine salts, **MAS-ER**: Extended-release mixed amphetamine salts, **METH**: Methamphetamine, **MA**: Meta-analysis**, N:** Number, **N/A**: Not applicable, **RCT**: Randomized controlled trial, **RoB:** Risk of Bias, **RR**: Risk Ratio, **SR**: Systematic Review, **UDS**: Urine Drug Screen,
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality)[ii]	Effect/Impact	Comments
Cocaine use	Critical	Moderate	Meta-analysis: Tardelli 2020[1] (High)	**Positive effect for MAS-ER + Topiramate.** Higher rate of UDS-confirmed 3+ weeks of continuous cocaine abstinence in MAS-ER + Topiramate compared to Placebo groups: 2 RCTs, n=208, RR = 2.45, 95% CI 1.29-4.65, p=0.006. • Levin 2020[2] (n=127 CoUD with more than moderate frequency baseline cocaine use [≥9 days/mo]); Mariani 2012[3] (n=81 CoUD with more than low frequency baseline cocaine use [≥4 days/mo])	
Treatment retention	Critical	Low	RCT: Levin 2020[2] (Supplemental)	**No effect.** No significant difference between MAS-ER + Topiramate and Placebo • n=127 CoUD, moderate or high baseline cocaine use (≥9 days/mo)	
			RCT: Mariani 2012[3] (Supplemental)	**No effect.** No significant difference between MAS-ER + Topiramate and Placebo • n=81 CoUD, more than low frequency baseline cocaine use (≥4 days/mo)	
Serious adverse events	Critical	Low	RCT Levin 2020[2] (Supplemental)	**No effect.** No significant difference between MAS-ER + Topiramate and Placebo. Four of 127 participants had serious adverse events (two in each treatment arm) • n=127 CoUD, moderate or high baseline cocaine use (≥9 days/mo)	
			RCT: Mariani 2012[3] (Supplemental)	**No effect.** No significant difference between MAS-ER + Topiramate and Placebo. Two of 81 participants had serious adverse events (one in each treatment arm) • n=81 CoUD, more than low frequency baseline cocaine use (≥4 days/mo)	
Cocaine craving	Important	Low	RCT: Levin 2020[2] (Supplemental)	**Positive effect for MAS-ER + Topiramate.** Craving scores decreased more rapidly over time in the MAS-ER + Topiramate group compared to placebo (time*treatment interaction, p<.001). • n=127 CoUD, moderate or high baseline cocaine use (≥9 days/mo)	
Adverse events	Important	Low	RCT: Levin 2020[2] (Supplemental)	**Negative effect for MAS-ER + Topiramate.** "Dry mouth was the only adverse event that was reported significantly more in the active medication group (16%, 10/64) versus the placebo group (5%, 3/63; p=.04)."	

				• n=127 CoUD, moderate or high baseline cocaine use (≥9 days/mo)	
			RCT: Mariani 2012[3] (Supplemental)	**Negative effect for MAS-ER + Topiramate.** "Moderate-to-severe adverse events reported by at least 5% of participants… Adverse effects that occurred significantly more frequently in the combined pharmacotherapy group included insomnia, changes in appetite, anxiety, irritability, paresathesias, and itching" • n=81 CoUD, more than low frequency baseline cocaine use (≥4 days/mo)	
Alcohol use (Co-occurring AUD)	Critical	N/A	Not found		
ADHD symptoms (Co-occurring)	Important	N/A	Not found		

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Levin 2020[2] (Supplemental)	RCT, double-blind 14 wks: 1 wk single-blind placebo lead-in, 12 wk medication phase, 1 wk taper USA Outpatient (2 sites)	(1) MAS-ER (up to 60 mg/day) + topiramate (up to 100 mg twice/day) (2) Placebo All participants received weekly compliance enhancement therapy (Brief Behavioral Compliance Enhancement Treatment (BBCET; Johnson, 2003) and rewards contingent on study attendance and compliance.	n=127 treatment seeking adults (18–60) with **CoUD** (DSM-IV-TR) with recent (≥1 day during lead-in week) and **moderate to high frequency (≥ 9 days in the prior month) baseline cocaine use.** 76% male, 23% white, 49% current AUD. Co-occurring ADHD not reported. Excluded: Current psychotic disorder other than transient psychosis due to drug abuse; unstable Axis I psychiatric disorder; prescribed psychostimulants or carbonic	**End of treatment continuous cocaine abstinence** (UDT & self-report, % n who achieved three consecutive abstinent weeks at the end of study): Higher treatment response rate in the treatment vs placebo group (9/64 [14.1%] vs 0/63 [0.0%], OR 19.9, 95% Ci 1.5–260.8, p=.03), while controlling for baseline cocaine use, sex, current AUD, and site. Baseline cocaine using days, sex, AUD, and site not significantly associated w/ tx response. Using the Haldane correction, the unadjusted odds ratio was 21.7 (95% CI 1.2-382.1). **Continuous cocaine abstinence:** Higher odds of any three consecutive weeks of cocaine abstinence during the study in the treatment group vs control group (14/64, 21.9% vs 4/63, 6.3%, OR 4.6, 95% CI 1.4–15.2, p=. 01). Baseline cocaine using days, sex, AUD, and site not significantly associated w/ outcome.	

			anhydrase inhibitors; history of seizures or unexplained loss of consciousness; significant current suicidal risk; opioid dependent; physiologically dependent on any other drugs (excluding nicotine or cannabis) which may require a medical detoxification; women who were pregnant, nursing, or unwilling to use adequate contraceptive methods; unstable physical disorders which made participation hazardous; history of glaucoma, kidney stones, or took any medications that were additive to the bicarbonate lowering effects of topiramate; history of failure to respond to a previous adequate trial of either of the candidate medications; legally mandated to receive SUD treatment; recent history (past 6 months) of a non-cocaine stimulant use disorder.	**Cocaine use:** Proportion of participants with positive weekly urine toxicology over time differed between groups (time*treatment interaction, p=0.004), while controlling for sex, current AUD, and site. The proportion of participants with positive UDT decreased over time in the treatment group (OR 0.92, 95%CI 0.87–0.99, p=.02), but not in the placebo group (p=0.07). **Treatment retention**: No significant difference in proportion of dropouts between groups (22/64 [34%] vs 26/63 [41%]). Time to dropout was not significantly different between the treatment and placebo groups (Hazard Ratio = 0.84; 95%CI 0.47–1.48; p=.54) while controlling for sex, current AUD, and site. **Craving**: Brief Substance Craving Scale (BSCS; Somoza et al., 1999): Scores decreased more rapidly in treatment compared to placebo groups (time*treatment interaction, p<.001). Craving scores in the treatment group decreased by 0.27 points/week (95%CI=0.24–0.31; p<.001), while in the placebo group, craving scores decreased by 0.15 points/week (95%CI=0.11–0.19; p<.001). **Adverse events**: Dry mouth was the only adverse event that was reported significantly more in the active medication group vs the placebo group (10/64 [16%] vs 3/63 [5%], p=.04). **Serious adverse events**: Four participants had serious adverse events (two in each treatment arm); however, none were deemed to be study-related. **Treatment adherence**: "In the treatment group, the median (IQR) of the within-participant proportion of samples positive for MAS-ER was 73% (47% −91%), and positive for topiramate was 100% (33%−100%)." (p. 9) **Discontinued medication early:** "due to conservative cardiac safety-parameters a considerable number of individuals in the treatment group were discontinued from study medication (20.3%)" (p. 2) 20.3% for MAS-ER, 25% for Topiramate, 20.3% for both	

				Dose reduction: In treatment group, 31% for MAS-ER, 18.8% for Topiramate, 9.4% for both	
Mariani 2012[3] (Supplemental)	RCT, double-blind 14 wks: 1 wk single-blind placebo lead-in, 12 wk medication phase, 1 wk taper USA Outpatient (1 site)	(1) MAS-ER (up to 60 mg/day) + topiramate (up to 150 mg twice/day) (2) Placebo All participants received a supportive behavioral intervention and rewards contingent on study attendance. 3 UDT/week.	n=81 treatment seeking adults (18-60) with **CoUD** (DSM-IV-TR) **with ≥ 4 days of cocaine use in prior 28 days**. 86% male, 31% white. Co-occurring AUD and ADHD not reported. Excluded: Major depressive disorder, psychotic disorder other than transient psychosis due to substance use; unstable Axis I psychiatric disorder; physiological dependence on any substances (other than cocaine, nicotine or cannabis) that would require medical intervention; prescribed psychotropic medication other than for insomnia; current diagnosis of psychostimulant abuse or dependence; significant risk for suicide; coronary vascular disease; unstable physical condition; history of seizures; history of an allergic reaction to MAS-ER (or other amphetamine analogs) or topiramate; pregnant or lactating; prescribed carbonic anhydrase inhibitors; history of glaucoma or kidney stones; history of failure to respond to either study medication; legally mandated to receive SUD treatment	**Continuous cocaine abstinence:** Higher odds of three consecutive weeks of cocaine abstinence during the study in the treatment group vs control group (13/39 [33.3%] vs 7/42 [16.7%]). Significant moderating effect of baseline severity of cocaine use (measured by cocaine use days at baseline; Wald $\chi 2=3.75$, df =1, p=.05) on outcome "suggesting that the combination treatment was most effective for participants with a high baseline frequency of cocaine use." (p. 1) eg, **for patients with baseline cocaine use days of at least 9 days or more (moderate to high severity),** abstinence rate in treatment group than placebo group (37.0% vs 7.4%, OR 7.4, 95% CI 1.4, 37.8). **Cocaine abstinence:** Weekly abstinence had a significant baseline cocaine using days by treatment interaction (p= .0062) and no significant effect of time. "The likelihood of abstinence was significantly greater on medication than placebo beginning at a baseline of about 10 days using cocaine per month, with the superiority of medication over placebo increase as baseline level of use increases." (p. 6) **Treatment retention**: No sig difference between groups (29/39 [74.4%] vs 35/42 [83.3%], $\chi 2=.98$, df =1, p=.32) **Adverse events**: "Moderate-to-severe adverse events reported by at least 5% of participants… Adverse effects that occurred significantly more frequently in the combined pharmacotherapy group included insomnia, changes in appetite, anxiety, irritability, parathesias, and itching." **Serious adverse events**: Two participants had serious adverse events (one in each treatment arm) **Treatment adherence**: No sig difference between groups (p=0.65). Ninety-three percent of the combined pharmacotherapy group participants had over 80% of their urine samples positive for amphetamine, and 89% of the combination medication group serum topiramate samples were positive.	ITT analysis

BSCS: Brief Substance Craving Scale; Somoza et al., 1999).

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
One high quality meta-analysis (Tardelli 2020)[1] found that MAS-ER + Topiramate treatment had a 2.45 higher likelihood of achieving a period of cocaine abstinence during the study compared to placebo. (2 RCTs, n=208, RR = 2.45, 95% CI 1.29-4.65, p=0.006). In one RCT, cocaine craving decreased more rapidly in treatment compared to placebo groups, by 0.27 vs 0.15 points/week (Levin 2020)[2].		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Considerations*	*Judgment*
		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Considerations*	*Judgment*
		☐ No studies ☐ Very low

		☐ Low ☒Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Considerations*	*Judgment*
		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
*** Equity**: What would be the impact on health inequities?		
Evidence Summary	*Considerations*	*Judgment*
	Both medications are available as low cost generics. However, this intervention is more likely to be prescribed by a specialist.	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Considerations*	*Judgment*
	There is still hesitance among some clinicians to prescribe an amphetamine in the treatment of stimulant use disorders. However, there are methods to mitigate the risk of misuse and diversion (see co-occurring ADHD stimulant medication	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Considerations*	*Judgment*
	Lower feasibility for combination medications. Prescription of a controlled substance also carries additional logistical barriers to patients and prescribers.	☐ No ☐ Probably no ☐ Uncertain

	As a controlled substance, MAS-ER may be subject to additional barriers	☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

Extended-release mixed amphetamine salts (MAS-ER)—such as Adderall and Mydayis—are composed of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and/or amphetamine sulfate. These medications increase the release of dopamine and norepinephrine and inhibit the reuptake of these neurotransmitters

Subgroup Considerations

None noted

Implementation Considerations

- Effective methods and processes of prescribing should consider the following factors:
    - Clinicians should regularly monitor patients being prescribed a controlled substance or with abuse potential for medication adherence and misuse (ie, non-medical use). This could include checking the PDPM, regular UDS.
    - In certain treatment settings, prescribing controlled substances may be problematic (eg, regulatory and monitoring issues, non-medical staff, non-stimulant treatment milieu)

Research Priorities

Research in patients with amphetamine/methamphetamine use disorder is needed.

References

1. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2020;237(8):2233-2255. doi:10.1007/s00213-020-05563-3
2. Levin FR, Mariani JJ, Pavlicova M, et al. Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users. *Drug Alcohol Depend*. 2020;206:107700. doi:10.1016/j.drugalcdep.2019.107700
3. Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence: A Randomized Controlled Trial. *Biol Psychiatry*. 2012;72(11):950-956. doi:10.1016/j.biopsych.2012.05.032

Table 15. Psychostimulant Amphetamines for Cocaine Use Disorder

Recommendation: For patients with cocaine use disorder, clinicians can consider prescribing a long-acting amphetamine formulation psychostimulant to promote cocaine abstinence.

a. Clinicians can give long-acting amphetamine formulation psychostimulants additional consideration for patients with co-occurring ADHD, as these medications can also reduce ADHD symptoms.
b. When prescribing a long-acting amphetamine formulation psychostimulant, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce cocaine use.

Clinical Question Summary Table

Clinical Question	Are long-acting amphetamine formulations of prescription psychostimulants safe and effective at reducing stimulant use and increasing treatment retention in patients with cocaine use disorder?
Population	Patients with cocaine use disorder
Intervention	Amphetamine formulation of prescription psychostimulants
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, adverse events, psychological symptoms, ADHD symptoms
Setting	Inpatient or outpatient
Considerations	Co-occurring ADHD
Background & Definitions	Dosing should be robust
Abbreviations	**ADHD:** Attention Deficit Hyperactivity Disorder, **ATS**: Amphetamine-type stimulants, **ATStUD**: Amphetamine-type stimulant use disorder, **CBT:** Cognitive behavioral therapy, **CM:** Contingency management, **CoUD**: Cocaine Use Disorder, **d-AMP**: Dexamphetamine, **ERMS-AMP**: Extended-release mixed amphetamine salts, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **MOD**: Modafinil, **MPH**: Methylphenidate, **N:** Number, **OUD:** Opioid use disorder, **RoB:** Risk of Bias, **RR:** Risk rate, **SMD:** Standard mean deviation, **UDS**: Urine Drug Screen
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Excludes direct comparisons of modafinil and bupropion (classified as a psychostimulant by some review authors, eg, Bhatt (2016), Castells (2016) individually to placebo. They are included in some authors' analysis of psychostimulants as a group.

Outcome	Strength of Evidence[i]	Sources (Quality)[ii]	Effect/Impact	Comments
Critically Important Outcomes				

Continuous stimulant abstinence	Low	Meta-analysis: Castells 2016[1] (Supplemental)	**Positive effect for prescription psychostimulants**: More patients with CoUD achieved sustained cocaine abstinence when treated with prescription psychostimulants compared to placebo: 14 RCTs, 1549 participants, RR (95% CI) = 1.36 (1.05, 1.77), p=0.02. Includes studies of:
			• Bupropion (2 studies)
			  • Poling 2006 (n=106 w/ OUD, Bupropion 300 mg/day); Shoptaw 2008 (n=73 MaUD, 12 wks Bupropion-SR 150 mg BID vs Placebo
			• Dexamphetamine (3 studies)
			  • Grabowski 2004a (n=120 w/ OUD, d-AMP SR max 60 mg/day); Shearer 2003 (n=30 w/ OUD, d-AMP-SR max 60 mg/day)
			• Selegiline transdermal patch (1 study)
			  • Elkashef (2006) (n=300
			• Mixed amphetamine salts (1 study)
			  • Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg)
			• Modafinil (5 studies)
			  • Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Schmitz 2014 (n=40, MOD 200-400 mg)
			• Methylphenidate (1 study)
			  • Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg)
			• Mazindol (1 study)
			  • Stine 1995
				Included bupropion and modafinil as psychostimulant. As well as other medications

		Meta-analysis: Tardelli 2020[2] (High)	**Positive effect for prescription psychostimulants.** Higher likelihood of 2–3 weeks of sustained abstinence in patients with CoUD treated with prescription psychostimulants compared to placebo: 15 RCTs, 1507 participants, RR (95% CI) = 1.7 (1.26, 2.31), p=0.001. Includes studies of:
			• Dexamphetamine (3 studies)
			  • Grabowski 2004a (n=120 w/ OUD, d-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, d-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, d-AMP-SR max 60 mg/day)
			• Dexamphetamine + modafinil (1 study)
			  • Schmitz 2012 (n=73, d-AMP 50 mg + MOD 200-400 mg/day)
			• Methylphenidate (3 studies)	

			• Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg) • Mixed amphetamine salts (1 study) • Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg) • Mixed amphetamine salts + topiramate (2 studies) • Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day) • Modafinil (5 studies) • Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Schmitz 2014 (n=40, MOD 200-400 mg) Subgroup analyses: **Dose:** **Positive effect for prescription psychostimulants at max dose.** Higher likelihood of 2–3 weeks of sustained abstinence in patients with CoUD treated with maximum FDA (for approved conditions) or higher doses of prescription psychostimulants compared to placebo: 12 studies, 1245 participants, RR (95% CI) = 1.95 (1.38, 2.77), p<0.001. Includes studies of: • Dexamphetamine (3 studies) • Grabowski 2004a (n=120 w/ OUD, D-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, D-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, D-AMP-SR max 60 mg/day) • Dexamphetamine + modafinil (1 study) • Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day) • Methylphenidate (1 study) • Levin 2006 (n=93 w/ ADHD, OUD, MPH-SR 10–80 mg/day) • Mixed amphetamine salts (1 study) • Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg) • Mixed amphetamine salts + topiramate (2 studies) • Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day) • Modafinil (4 studies)	

			• Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg) ; Schmitz 2014 (n=40, MOD 200-400 mg) **No effect for low dose prescription psychostimulants**. No significant difference in likelihood of 2–3 weeks of sustained abstinence between CoUD patients treated with prescription psychostimulants and placebo when psychostimulants doses were lower than FDA's maximum recommended doses: 4 RCTs, 472 participants, RR (95% CI) = 1.25 (0.71, 2.21), p=0.44. Includes studies of: • Methylphenidate (2 studies) • Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg) • Modafinil (2 studies) • Dackis 2012 (n=210, MOD SR 200-400 mg); Kampman 2015a (n=94, MOD 300 mg) **<u>Co-occurring Opioid Use Disorder (OUD):</u>** **Positive effect for prescription amphetamines in patients with co-occurring OUD.** Higher likelihood of 2–3 weeks of sustained abstinence in patients with CoUD and co-occurring OUD treated with prescription amphetamines compared to placebo: 3 studies RR (95% CI) = 2.46 (1.43, 4.24). 1. Grabowski 2004a (n=120 w/ OUD, D-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, D-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, D-AMP-SR max 60 mg/day) **Positive effect for prescription amphetamines in patients without co-occurring OUD.** Higher likelihood of 2–3 weeks of sustained abstinence in patients with CoUD without co-occurring OUD treated with prescription amphetamines compared to placebo: 4 studies RR (95% CI) = 2.41 (1.39, 4.17) 2. Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day) **<u>Co-occurring Attention Deficit Hyperactivity Disorder (ADHD):</u>** **Positive effect for prescription psychostimulants in patients without co-occurring ADHD.** Higher likelihood of 2–3 weeks of sustained abstinence in patients with CoUD or ATStUD without co-occurring ADHD treated with prescription psychostimulants	

			compared to placebo: 14 RCTs, 1463 participants, RR (95% CI) = 1.55 (1.14, 2.11), p= 0.006. Includes studies of: 3. Amphetamine-type stimulant use disorder (2 studies) • Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day) 4. Cocaine use disorder (12 studies) • Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day); Grabowski 2004a (n=120 w/ OUD, D-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, D-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, D-AMP-SR max 60 mg/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Schmitz 2014 (n=40, MOD 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg) **No effect in patients with co-occurring ADHD.** No significant difference between prescription psychostimulants and placebo groups in likelihood of 2–3 weeks of sustained abstinence in patients with CoUD or ATStUD and co-occurring ADHD: 4 RCTs, 349 participants, RR (95% CI) = 1.17 (0.61, 2.25), p= 0.63. Includes studies of: • Amphetamine-type stimulant use disorder (1 study) • Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg) • Cocaine use disorder (3 studies) • Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day); Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day); Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg)	
Stimulant use	Moderate	Meta-analysis: Bentzley 2021[3] (Low)	**Positive effect for prescription psychostimulants**. Psychostimulant groups had lower odds of cocaine use (UDS+) at end of trial in patients with cocaine use disorder**:** 13 RCTs, 645 participants, OR (95% CI) = 2.48 (1.27, 4.85), p=0.008. Higher odds ratio means greater reduction in cocaine use (greater likelihood of negative UDS). Dackis (2005), Dackis (2012), Dursteler-MacFarland (2013), Grabowski (2004a), Grabowski (2001), Grabowski (1997), Levin (2015a), Levin (2007), Mooney (2009), Mooney (2015), Schubiner (2002), Shearer (2003)	Multilevel meta-analysis including covariates: Age, gender, cocaine use (d/wk), cocaine history (y), ASI drug subscale, % abstinent at baseline, treatment duration (wk)
		Meta-analysis: Tardelli 2020[2] (High)	**Positive effect for prescription amphetamine**. Higher percentage of drug-negative urine tests across trial in cocaine use disorder patients treated with Prescription	

			amphetamine compared to placebo: 6 RCTs, 557 participants, MD (95% CI) = 8.37 (3.75, 12.98), p=<0.001. Included studies of:
			• Dexamphetamine (3)
			  • Grabowski 2004a (n=120 w/ OUD, d-AMP-SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, d-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, d-AMP-SR max 60 mg/day)
			• Mixed amphetamine salts (1)
			  • Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg)
			• Mixed amphetamine salts + topiramate (2)
			  • Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day)	

		Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in mean proportion of cocaine-free urinalyses across the study per patient in patients with cocaine use disorder treated with prescription psychostimulants vs placebo: 8 studies, 526 participants: • Grabowski (1997), Grabowski (2004a), Levin (2007), Morgan (2016), Poling (2006), Schubiner (2002), Shearer (2003), Shoptaw (2008b)	Included bupropion and modafinil as psychostimulant as well as other medications However, 2 recent studies not included, Konstenius et al. 2014 and Levin et al. 2015 but Konstenius was methylphenidate
		Meta-analysis: Chan 2020[4] (Moderate-high)	**No effect.** No significant difference in cocaine-free UDS in patients with cocaine use disorder and co-occurring **OUD** treated with prescription psychostimulants vs placebo. 3 RCTs, 115 participants, SMD (95% CI) = 0.35 (-0.5, 0.74), p=0.08. • Grabowski 2004a (n=120 w/ OUD, d-AMP-SR max 60 mg/day); Margolin 1995a (n=37 w/ OUD abstinent for 2 wks, Mazindol); Margolin 1997 (n=17 w/ OUD, Mazindol 1 or 8 mg/day)	
		Systematic review: Cook 2017[5] (Moderate)	**Mixed results.** "Two of six studies that reported substance use outcomes showed significant improvement for treatment arms compared with placebo (Konstenius et al., 2014; Levin et al., 2015)" (Cook, 2017).	
Treatment retention	High	Meta-analysis: Tardelli 2020[2] (High)	**No effect.** No significant difference between prescription psychostimulants and placebo in treatment retention between cocaine use disorder patients treated with: 24 RCTs, 2195 participants, RR (95% CI) = 1.03 (0.96, 1.11), p=0.390. Includes studies of: • Dexamphetamine • Nuijten 2016 (n=73 w/ OUD, D-AMP 60 mg/day); Grabowski 2001 (n=128, D-AMP SR max 60 mg/day); Grabowski 2004a (n=120 w/	

			OUD, D-AMP SR max 60 mg/day); Shearer 2003 (n=30 w/ OUD, D-AMP-SR max 60 mg/day); Mooney 2015 (n=43, L-D-AMP 70 mg)
			• Dexamphetamine + modafinil
			  • Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day)
			• Methylphenidate
			  • Schubiner 2002 (n=43 w/ ADHD, MPH 30–90 mg); Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Grabowski 1994 (n=7, MPH max 45 mg/day); Grabowski 1997 (n=49, MPH max 45 mg/day); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg)
			• Mixed amphetamine salts
			  • Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg)
			• Mixed amphetamine salts and topiramate
			  • Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day)
			• Oral methamphetamine
			  • Mooney 2009 (n=82, Regular and SR oral methamphetamine max 30 mg/day)
			• Modafinil
			  • Schmitz 2014 (n=40, MOD 200-400 mg); Sofuoglu 2021 NCT00838981 (n=91 w/ OUD, MOD 200-400 mg); Schmitz NCT00218036 (n=51 w/ OUD, MOD 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Kampman 2020; (n=164 w/ AUD, MOD 400 mg/day or MOD 400 mg/day + Naltrexone 150 mg daily for males; 100 mg daily for females); Malcolm 2009 NCT00218387 (n=123, MOD 400 mg); Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg)
			• Modafinil and naltrexone
			  • Kampman 2020; (n=164 w/ AUD, MOD 400 mg/day or MOD 400 mg/day + Naltrexone 150 mg daily for males; 100 mg daily for females)	

		Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in retention in cocaine use disorder treatment for prescription psychostimulants vs placebo: 24 RCTs, 2205 participants, RR (95% CI) = 1 (0.93, 1.06), p=0.91.	Included bupropion and modafinil as psychostimulant as well as other medications

		Meta-analysis: Chan 2020[4] (Moderate-high)	**No effect.** No significant difference in retention in patients with cocaine use disorder and co-occurring OUD between prescription psychostimulants vs placebo: 4 RCTs, 210 participants, RR (95% CI) = 0.98 (0.71, 1.36), p=0.91. • Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Grabowski 2004a (n=120 w/ OUD, D-AMP SR max 60 mg/day); Margolin 1995b (Mazindol); Margolin 1997 (Mazindol)	
Dropout due to adverse events	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in rate of dropout due to adverse events for patients with cocaine use disorder treated with prescription psychostimulants vs placebo: 18 RCTs, 1601 participants, RD (95% CI) = 0 (-0.01, 0.01), p=0.84	Included bupropion and modafinil as psychostimulant as well as other medications
Important Outcomes				
Adverse events	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in number of patients experiencing any serious adverse events in patients with cocaine use disorder treated with prescription psychostimulants vs placebo: 6 RCTs, 444 participants: • Dackis 2005 (n=62, MOD SR 400 mg); Kampman 2015a (n=94, MOD 300 mg); Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg); Mooney 2015 (n=43, L-D-AMP 70 mg); Kampman 2020 (NCT00142818); Schmitz (2014)	Included bupropion and modafinil as psychostimulant as well as other medications This is considering a broad definition of stimulants
		Systematic review: Cook 2017[5] (Moderate)	**Negative effect for MAS-ER.** "Dry mouth was the only adverse event that occurred significantly more frequently in the group receiving extended-release mixed amphetamine salts compared with placebo (Levin et al., 2015)" (Cook, 2017).	This is only one study
Stimulant craving	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in cocaine craving for patients with cocaine use disorder treated with prescription psychostimulants vs placebo: 6 RCTs, 532 participants: • Elkashef (2006); Margolin (1995); Mooney (2015); Perry (2004); Shoptaw (2008); Stine (1995)	Included bupropion and modafinil as psychostimulant as well as other medications
Co-occurring ADHD symptoms	Moderate	Meta-analysis: Castells 2016[1] (Supplemental)	**No effect.** No significant difference in ADHD symptom severity for patients with cocaine use disorder treated with prescription psychostimulants vs placebo: 3 RCTs, 247 participants: Levin (2007), Levin (2015a), Schubiner (2002)	Included bupropion and modafinil as psychostimulant as well as other medications
		Systematic review: Cook 2017[5] (Moderate)	**Mixed results.** "Four of eight studies reporting ADHD outcome measures showed significant improvement in ADHD outcome measures compared with placebo." (Cook, 2017). • Ginsberg and Lindefors, 2012; Konstenius et al., 2014; Levin et al., 2015; Schubiner et al., 2002	Need to take into account dosing and formulation. Longer acting formulations at higher dosing may be needed

		Cross-sectional study: Manni 2019[6] (Unclear RoB)	**Cocaine use and CoUD symptoms decreased during the stimulant treatment of A-ADHD,** and were not correlated with age, gender, familiarity, length of treatment, or medication used. CUD improvement was closely correlated with A-ADHD improvement, Manni (2019).	But I believe it may have been correlated with dosing? I believe the Manni study is MPH?

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Existing Guidelines

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Tardelli's meta-analysis is the most thorough to date and only includes 3 medications and looks at the evidence separately for each medication and for CoUD and MaUD. The research evidence is promising for amphetamine formulations for CoUD but more work is needed. Based on several RCTs (Levin 2015) Grabowski, Nyugen	Trials may fail due to under-dosing or adherence. Formulations Mooney DAD long-acting > IR	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
When monitored closely and there are conservative parameters for holding doses or drop out, a substantial minority of patients will not be able to be on robust doses. However, serious advee low. Good cardiovascular screening at baseline is important. Several investigators have found that abuse potential is low	Known effects on blood pressure can be managed by close patient monitoring and dose adjustment.	☐ None ☒ Small ☐Moderate ☐ Large ☐ Varies

		☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
		☐Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence Summary	*Additional Considerations*	*Judgment*
At present, robust dosing and facilitation of abstinence seems to favor amphetamine formulations		☐ Clinical judgment (no evidence) ☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Research Evidence Summary	*Additional Considerations*	*Judgment*
It depends on whether the focus is on abstinence, reduction in use, craving or retention. At present, abstinence remains the gold standard, and only clear evidence of amphetamine formulations outperforming placebo for CoUD with this outcome measure		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Uncertain
***** **Equity**: What would be the impact on health inequities?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	It may be harder for minority populations to access medication interventions. On the other hand, medications can be provided in medical settings and might be easier for all patients to access, if prescribers are comfortable	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced

	prescribing medications than referring patients for psychosocial interventions	☐ Reduced ☒ Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
There is very limited evidence regarding this question.		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
Stigma is a huge issue re: access to treatment. For FDA-approved medications for alcohol use disorder, less than 10% receive them. It is better for OUD but still most do not receive MOUD. Thus, there remains a lot of work to do.	It should be feasible given that psychostimulants are approved medications for other disorders but unless they are FDA-approved for this indication, many providers may feel (and not unreasonably so) uncomfortable to use them	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

For select populations, amphetamine long-acting formulations might be useful for those with CoUD
Tardelli provides the best overview to date.
Certainty of evidence is moderate for long acting-amphetamine formulations for Cocaine Use Disorder

Subgroup Consideration

- May work best for those with ADHD if dosing is adequate
- May work best if adequate baseline severity of frequency of use

Implementation Considerations

- Robust dosing may be needed. Consider going to the maximum tolerated dose.
- Close monitoring is needed and whether patient has past misuse/abuse of prescriptions stimulants
- Good cardiovascular screening at baseline is important. Need to do good baseline assessment of cardiovascular stability and monitor cardiovascular sxs, blood pressure, HR, ECG intermittently throughout early phase of treatment
- Risk of diversion and misuse can be managed (see Co-occurring ADHD section)

References

1. Castells X, Cunill R, Pérez-Mañá C, Vidal X, Capellà D. Psychostimulant drugs for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 27, 2016. doi:10.1002/14651858.CD007380.pub4
2. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2020;237(8):2233-2255. doi:10.1007/s00213-020-05563-3
3. Bentzley BS, Han SS, Neuner S, Humphreys K, Kampman KM, Halpern CH. Comparison of Treatments for Cocaine Use Disorder Among Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2021;4(5):e218049. doi:10.1001/jamanetworkopen.2021.8049
4. Chan B, Freeman M, Ayers C, et al. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. *Drug Alcohol Depend*. 2020;216:108193. doi:10.1016/j.drugalcdep.2020.108193
5. Cook J, Lloyd-Jones M, Arunogiri S, Ogden E, Bonomo Y. Managing attention deficit hyperactivity disorder in adults using illicit psychostimulants: A systematic review. *Aust N Z J Psychiatry*. 2017;51(9):876-885. doi:10.1177/0004867417714878
6. Manni C, Cipollone G, Pallucchini A, Maremmani AGI, Perugi G, Maremmani I. Remarkable Reduction of Cocaine Use in Dual Disorder (Adult Attention Deficit Hyperactive Disorder/Cocaine Use Disorder) Patients Treated with Medications for ADHD. *Int J Environ Res Public Health*. 2019;16(20):3911. doi:10.3390/ijerph16203911
7. Brandt L, Chao T, Comer SD, Levin FR. Pharmacotherapeutic strategies for treating cocaine use disorder-what do we have to offer? *Addiction*. 2021;116(4):694-710. doi:10.1111/add.15242

Table 16. Psychostimulant Methylphenidate for Amphetamine-Type Stimulant Use Disorder

Recommendation: For patients with amphetamine-type StUD, clinicians can consider prescribing a long-acting methylphenidate formulation to promote reduced use of amphetamine-type stimulants.

a. Clinicians can give long-acting methylphenidate formulations additional consideration for patients with moderate or higher frequency of ATS use at treatment start (eg, 10+ days/month).
b. Clinicians can give long-acting methylphenidate formulations additional consideration for patients with co-occurring ADHD, as they can also reduce ADHD symptoms.
c. When prescribing a long-acting methylphenidate formulation, clinicians can consider dosing at or above the maximum dose approved by the FDA for the treatment of ADHD to effectively reduce amphetamine-type stimulant use.

Clinical Question Summary Table

Clinical Question	Are long-acting methylphenidate formulations or prescription psychostimulants safe and effective at reducing stimulant use and increasing treatment retention in patients with amphetamine-type stimulant use disorder?
Population	Patients with amphetamine-type stimulant use disorder
Intervention	Long-acting methylphenidate formulation prescription psychostimulants
Comparison	Placebo
Main Outcomes	Stimulant use, treatment retention, stimulant craving, adverse events, psychological symptoms, ADHD symptoms
Setting	Inpatient or outpatient
Considerations	Co-occurring ADHD
Background & Definitions	Dosing should be robust Notes • What do these medications do? • Why would we expect this treatment to benefit patients w/ StUD? • General dosing information/examples
Abbreviations	**ADHD:** Attention Deficit Hyperactivity Disorder, **ATS**: Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CBT:** Cognitive behavioral therapy, **CM:** Contingency management, **CoUD**: Cocaine Use Disorder, **D-AMP**: Dexamphetamine, **ERMS-AMP**: Extended-release mixed amphetamine salts **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder **MOD**: Modafinil, **MPH**: Methylphenidate, **N:** Number, **RoB:** Risk of Bias, **RR:** Risk rate, **SMD:** Standard mean difference, **UDS**: Urine Drug Screen, **OUD:** Opioid use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Sources (Quality)[ii]	Effect/Impact	Comments
Outcome Importance: Critical				
Continuous stimulant abstinence	Low	Meta-analysis: Tardelli 2020[1] (High)	**No effect.** No significant difference in likelihood of 2–3 weeks of sustained stimulant abstinence between amphetamine-type stimulant use disorder patients treated with prescription psychostimulants vs placebo: 3 RCTs, n=305, RR (95% CI) = 0.89 (0.62, 1.27), p=0.53. Included studies of: • Methylphenidate (1 RCT) o Konstenius 2010 (n=24 ATStUD w/ ADHD, MPH-SR 18–72 mg titrated) • Modafinil (2 RCTs) o Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day titrated) **No effect.** No significant difference in likelihood of 2–3 weeks of sustained stimulant abstinence between cocaine OR amphetamine-type stimulant use disorder patients treated with methylphenidate vs placebo in**:** 4 RCTs, n=285, RR (95% CI) = 0.9 (0.6, 1.37), p= 0.63. Included studies of: • Amphetamine-type use disorder (1 RCT) o Konstenius 2010 (n=24 ATStUD w/ ADHD, MPH-SR 18–72 mg titrated) • Cocaine use disorder (3 RCTs) o Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg titrated); Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day titrated) **Subgroup analyses:** **Dose:** **Positive effect for prescription psychostimulant at max dose.** Higher likelihood of 2–3 weeks of sustained abstinence in CoUD or ATStUD patients treated with FDA's maximum recommended (for approved conditions) or higher doses of prescription psychostimulants compared to placebo: 15 RCTs, n=1550, RR (95% CI) = 1.5 (1.1, 2.06), p= 0.01. Included studies of: • Amphetamine-type stimulant use disorder (3 RCTs)	For the MaUD studies with long-acting methylphenidate, may need higher dosing and more effective in frequent users.

			○ Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day); Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg) • Cocaine use disorder (12 RCTs) ○ Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dackis 2012 (n=210, MOD SR 200- 400 mg); Grabowski 2004a (n=120 w/ OUD, d-AMP SR max 60 mg/day); Levin 2006 (n=93 w/ ADHD, OUD, MPH-SR 10–80 mg/day + Bupropion SR 100–400 mg/day); Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Nuijten 2016 (n=73 w/OUD, d-AMP 60 mg/day); Schmitz 2012 (n=73, d-AMP 50 mg + MOD 200-400 mg/day); Schmitz 2014 (n=40, MOD 200-400 mg); Shearer 2003 (n=30 w/ OUD, d-AMP-SR max 60 mg/day) **No effect for low dose prescription psychostimulants**. No significant difference in likelihood of 2–3 weeks of sustained abstinence between CoUD or ATStUD patients treated with prescription psychostimulants and placebo when psychostimulants dose is lower than FDA's maximum recommended doses: 4 RCTs, n=472, RR (95% CI) = 1.25 (0.71, 2.21), p= 0.44. • All included studies of patients with cocaine use disorder (4 RCTs) ○ Dackis 2012 (n=210, MOD SR 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg) **<u>Co-occurring Opioid Use Disorder (OUD):</u>** **Positive effect for prescription psychostimulants in patients with co-occurring OUD.** Higher likelihood of 2–3 weeks of sustained abstinence between cocaine OR amphetamine-type stimulant use disorder patients with co-occurring OUD treated with prescription psychostimulants vs placebo in participants: 5 RCTs, 378 participants, RR (95% CI) = 2.03 (1.24, 3.33), p=0.005. • All included studies of patients with cocaine use disorder (5 RCTs) ○ Grabowski 2004a (n=120 w/ OUD, d-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, d-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, d-AMP-SR max 60 mg/day); Dursteler-MacFarland 2013 (n=62 w/	

			OUD, MPH 60 mg); Levin 2006 (n=93 w/ ADHD, OUD, MPH-SR 10–80 mg/day) **No effect in patients without OUD**. No significant difference in likelihood of 2–3 weeks of sustained abstinence between cocaine OR amphetamine-type stimulant use disorder patients without co-occurring OUD treated with prescription psychostimulants vs placebo: 13 RCTs, 1434 participants, RR (95% CI) = 1.34 (0.98, 1.83), p=0.07. • Amphetamine-type stimulant use disorder (3 RCTs) o Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day); Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg) • Cocaine use disorder (10 RCTs) o Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day); Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Levin 2007 (n=106 w/ ADHD, MPH-SR 10–60 mg); Schmitz 2014 (n=40, MOD 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg) **<u>Co-occurring Attention Deficit Hyperactivity Disorder (ADHD):</u>** **No effect for patients with co-occurring ADHD.** No significant difference in likelihood of 2–3 weeks of sustained abstinence between cocaine OR amphetamine-type stimulant use disorder patients with co-occurring ADHD treated with prescription psychostimulants vs placebo: 4 RCTs, 349 participants, RR (95% CI) = 1.17 (0.61, 2.25), p= 0.63. • Amphetamine-type stimulant use disorder (1 RCT) o Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg) • Cocaine use disorder (3 RCTs) o Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day); Levin 2006 (n=93 w/ ADHD & OUD, MPH-SR 10–80 mg/day); Levin 2015a (n=126 w/ ADHD, MAS-ER 60-80 mg) **Positive effect for prescription psychostimulants in patients without co-occurring ADHD.** Higher likelihood of 2–3 weeks of sustained abstinence between cocaine OR amphetamine-type stimulant use disorder patients without co-occurring ADHD treated with prescription psychostimulants vs placebo: 14 RCTs, 1463 participants, RR (95% CI) = 1.55 (1.14, 2.11), p= 0.006.	

			• Amphetamine-type stimulant use disorder (2 RCTs)
			  ○ Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day)
			• Cocaine use disorder (12 RCTs)
			  ○ Schmitz 2012 (n=73, D-AMP 50 mg + MOD 200-400 mg/day); Grabowski 2004a (n=120 w/ OUD, D-AMP SR max 60 mg/day); Nuijten 2016 (n=73 w/ OUD, D-AMP 60 mg/day); Shearer 2003 (n=30 w/ OUD, D-AMP-SR max 60 mg/day); Mariani 2012 (n=81, MAS-ER 60 mg/day + Topiramate 150 mg twice/day); Levin 2020 (n=127, MAS-ER max 60 mg/day + Topiramate max 100 mg twice/day); Schmitz 2014 (n=40, MOD 200-400 mg); Kampman 2015a (n=94, MOD 300 mg); Anderson 2009 (n=210, MOD SR 200-400 mg); Dackis 2012 (n=210, MOD SR 200-400 mg); Dackis 2005 (n=62, MOD SR 400 mg); Dursteler-MacFarland 2013 (n=62 w/ OUD, MPH 60 mg)	

Stimulant use	Moderate	Meta-analysis: Tardelli 2020[1] (High)	**No effect.** No significant difference in patients with an amphetamine-type stimulant use disorder in the percentage of drug-negative urine tests across trial between groups treated with prescription psychostimulants vs placebo: 4 RCTs, 365 participants, MD (95% CI) = 0.14 (-1.86, 2.15), p=0.89. Included studies of:
			• Dexamphetamine (1 RCT)
			  ○ Galloway 2011 (n=60, d-AMP-SR 30 mg twice/day)
			• Mixed amphetamine salts (1 RCT)
			  ○ Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg)
			• Modafinil (2 RCTs)
			  ○ Anderson 2012 (n=210, MOD 200-400 mg/day); Heinzerling 2010 (n=71, MOD 400 mg/day)	

		Systematic review: Siefried 2020[2] (High)	**Positive effect for Methylphenidate.** Lower self-reported MA use in the methylphenidate arm compared with placebo was reported in a study (n = 110) that concurrently used CBT and CM [48]; and reductions in craving and MA-positive UDS was reported in a study enrolling 56 participants [54].” • [48] Ling 2014 (n=110, MPH-SR 54 mg/day) Self-reported MA use • [54] Rezaei 2015 (n=56, MPH-SR 54 mg/day) MA-pos UDS **Positive effect for Methylphenidate. Methylphenidate > Aripiprazole** • Tiihonen 2007 (n=53, MPH-SR 54 mg/day) MPH > Aripiprazole MA-pos UDS	I believe the difference for the Ling study was at 6 weeks but not 12 weeks? Need to check. The difference for self-reported use was significant when baseline use considered
		Systematic review: Lee	**Positive effect for Methylphenidate.** Methylphenidate shows “some benefit in reducing ATS [amphetamine-type stimulant] use” in patients with ATStUD (Lee, 2008).	Also, the Tardelli meta-analysis distinguished

		2018[3] (Moderate)	• Ling 2014 (n=110, MPH-SR 54 mg/day); Miles 2013 (n=79, MPH 54 mg/day); Minarik 2016 (n=24, MPH short acting, mean 37.6 mg/day); Rezaei 2015 (n=56, MPH-SR 54 mg/day); Solhi 2014 (n=86, MPH 10 mg/day max); Tiihonen 2007 (n=53, MPH-SR 54 mg/day) **No effect.** No significant difference between dexamphetamine and placebo in reduced stimulant use in patients with ATStUD. • Charnaud & Griffiths 1998 (n=180, d-AMP individualized dose); Galloway 2011 (n=60, d-AMP-SR 30 mg twice/day); Longo 2010 (n=49, d-AMP-SR 110 mg/day max); Merrill 2005 (n=59, d-AMP 100 mg/day max); Shearer 2001 (n=41, d-AMP 60 mg max); White 2000 (n=148, d-AMP 90 mg max); White 2006 w/ Pregnant women, d-AMP 30-60 mg)	cocaine from methamphetamine. This does not seem to be the case with this review? Adequate dosing and baseline use may need to be taken into account along with retention particularly for studies using methylphenidate

Treatment retention	High	Meta-analysis: Tardelli 2020[1] (High)	**No effect.** No significant difference for patients with amphetamine-type stimulant use disorder in treatment retention between groups treated with prescription psychostimulants vs placebo: 12 RCTs, 855 participants, RR (95% CI) = 1.08 (0.93, 1.27), p=0.320. Included studies of:
			• Dexamphetamine (2 RCTs)
			  ○ Galloway 2011 (n=60, d-AMP-SR 30 mg twice/day); Longo 2010 (n=49, d-AMP-SR max 110 mg/day)
			• Modafinil (4 RCTs)
			  ○ Anderson 2012 (n=210, MOD 200-400 mg/day); Mancino 2011 (n=9, MOD 400 mg); Heinzerling 2010 (n=71, MOD 400 mg/day); Shearer 2009 (n=80, MOD-SR max 200 mg/day)
			• Methylphenidate (6 RCTs)
			  ○ Miles 2013 (n=79 w/ Depression, MPH 54 mg/day); Konstenius 2014 (n=54 w/ ADHD, MPH-SR 18–180 mg); Konstenius 2010 (n=24 w/ ADHD, MPH-SR 18–72 mg); Tiihonen 2007 (n=53, MPH-SR 54 mg/day); Rezaei 2015 (n=56, MPH-SR 54 mg/day); Ling 2014 (n=110, MPH-SR 54 mg/day)	

		Systematic review: Siefried 2020[2] (High)	**Positive effect for Methylphenidate.** One study demonstrating higher retention rates in methylphenidate arms compared with placebo "was limited by a heterogeneous study sample" • [51] Miles 2013 (n=79 w/ Depression, MPH 54 mg/day)	
Outcome Importance: Important				

Stimulant craving	Moderate	Systematic review: Siefried 2020[2] (High)	**Positive effect for Methylphenidate.** Methylphenidate > placebo in reductions in craving." • Rezaei 2015 (n=56, MPH-SR 54 mg/day)	
		Systematic review: Lee 2018[3] (Moderate)	**Positive effect for Methylphenidate.** Methylphenidate "appears to reduce craving" (Lee, 2008). • Ling (2014), Miles (2013); Minarik (2016, Rezaei (2015); Solhi (2014); Tiihonen (2007)	
Co-occurring ADHD symptoms	Moderate	Systematic review: Cook 2017[4] (Moderate)	**Mixed results.** "Four of eight studies reporting ADHD outcome measures showed significant improvement in ADHD outcome measures compared with placebo" (Cook, 2017). • Ginsberg and Lindefors, 2012; Konstenius et al., 2014; Levin et al., 2015; Schubiner et al., 2002	Need to take into account dosing and formulation. Longer acting formulations at higher dosing may be needed

i: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Tardelli's meta-analysis is the most thorough to date and only includes 3 medications and looks at the evidence separately for each medication and for CoUD and MaUD. The research evidence is promising for amphetamine formulations for CoUD but more work is needed and 2 of the promising studies, including topiramate as well. The MPH studies for MaUD are somewhat promising but more work is needed at higher dosing. Similarly the use of amphetamine formulations for MaUD Is plagued by low doses and high-drop out	Trials may fail due to under-dosing, baseline level of use, or adherence. MPH is approved for ADHD treatment. Prior research suggests that higher doses of stimulant medications may be more effective than lower doses for the treatment of StUD.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Considerations*	*Judgment*
When monitored closely and there are conservative parameters for holding doses or drop out, a substantial minority of patients will not be able to be on robust doses. However, serious	Known effects on blood pressure can be managed by close patient monitoring and dose adjustment.	☐ None ☒ Small ☐ Moderate

adverse events are low. Several investigators have found that abuse potential is low	There is a potential for misuse and diversion.	☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Considerations*	*Judgment*
		☐Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Considerations*	*Judgment*
There is more confidence with MPH for ATStUD than for CoUD.	The CDC argues that evidence strength seems to depend on dosing. Therefore, the certainty of evidence…	☐ Clinical judgment (no evidence) ☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Considerations*	*Judgment*
.	It depends on whether the focus is on abstinence, reduction in use, craving or retention. At present, abstinence remains the gold standard	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Uncertain
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Considerations*	*Judgment*
	It may be harder for minority populations to access medication interventions. On the other hand, medications	☐ Increased ☐ Probably increased

	can be provided in medical settings and might be easier for all patients to access, if prescribers are comfortable prescribing medications than referring patients for psychosocial interventions	☐ Uncertain ☐ Probably reduced ☐ Reduced ☒Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Considerations*	*Judgment*
There is very limited evidence regarding this question. I am currently engaged in a study looking at this question but the data are not yet available. SO uncertain for now		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Considerations*	*Judgment*
Stigma is a huge issue re: access to treatment. For FDA-approved medications for alcohol use disorder, less than 10% receive them. It is better for OUD but still most do not receive MOUD. Thus, there remains a lot of work to do.	It should be feasible given that psychostimulants are approved medications for other disorders but unless they are FDA-aproved for this indication, many providers may feel (and not unreasonably so) uncomfortable to use them	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

For select populations MPH long-acting formulations might be useful for ATStUD.
Tardelli 2020[1] and Siefried 2020[2] provide the best overview to date for ATStUD.

Certainty of evidence

Weaker than moderate support for MPH long-acting formulation for ATStUD.

Subgroup Consideration

- May work best for those with ADHD if dosing is adequate.
- May work best if adequate baseline severity of frequency of use.

Implementation Considerations

- Robust dosing may needed. Consider going to the maximum tolerated dose.
- Close monitoring of medication adherence is needed, especially for patients with a history of misuse/abuse of prescriptions stimulants.
- Good cardiovascular screening at baseline is important. Need to do good baseline assessment of cardiovascular stability and monitor cardiovascular signs and symptoms, blood pressure, HR, ECG intermittently throughout early phase of treatment.
- Risk of diversion and misuse can be reduced (see Co-occurring ADHD section)
- Methylphenidate has previously caused false positives for amphetamine on immunoassay tests (eg. Manzi 2002[5]). However, false positives can be ruled out with confirmatory testing and does not occur in currently available immunoassays. Refer to the test manufacturer to determine the tests' capabilities and the cross-reactivity of the assay you are using.
- Methylphenidate can be detected with a toxicology test for its metabolite ritilynic acid. It can be included as part of routine clinical drug testing to monitor medication use.

References

1. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2020;237(8):2233-2255. doi:10.1007/s00213-020-05563-3
2. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
3. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018;191:309-337. doi:10.1016/j.drugalcdep.2018.06.038
4. Cook J, Lloyd-Jones M, Arunogiri S, Ogden E, Bonomo Y. Managing attention deficit hyperactivity disorder in adults using illicit psychostimulants: A systematic review. *Aust N Z J Psychiatry*. 2017;51(9):876-885. doi:10.1177/0004867417714878
5. Manzi S, Law T, Shannon MW. Methylphenidate produces a false-positive urine amphetamine screen. *Pediatr Emerg Care*. 2002;18(5):401. https://doi.org/10.1097/00006565-200210000-00019

Co-occurring Disorders

Table 17. Integrated Care

Recommendation: Clinicians should use an integrated behavioral treatment approach that addresses both conditions when available. Otherwise, clinicians should tailor a recommended behavioral therapy for StUD (eg, CM, CBT, CRA) to address possible interactions between a patient's StUD and co-occurring disorder(s).

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate behavioral interventions for the treatment of stimulant use disorder in patients with co-occurring psychiatric disorders? 2. What contextual factors and implementation strategies may influence the effects of behavioral interventions?
Population	Patients with co-occurring disorders
Intervention	Integrated care
Comparison	TAU or separate treatment for StUD and co-occurring disorder(s)
Main Outcomes	StUD symptoms, Co-occurring disorder symptoms
Setting	Outpatient
Background & Definitions	Only most common and/or problematic co-occurring psychiatric disorders known to be caused by and/or exacerbated by StUDs, including psychosis, depression, and anxiety
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **AUD**: Alcohol use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MDD**: Major depressive disorder, **N**: Number, **PTSD**: Post-traumatic Stress Disorder, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **SUD**: Substance use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Severe mental illness (Mixed diagnoses): Individual Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Bellack 2006[1]	RCT 6 mo USA Community clinics and VA medical centers	(1) **CBT + MI**: Behavioral Treatment for Substance Abuse in severe and persistent mental illness (SPMI) (2) **TAU:** standard care: Supportive Treatment for	N=175 38% DSM-IV **schizophrenia** or schizoaffective disorder, 55% **major affective disorder** and **substance** abuse or dependence (DSM-IV). Primary drug of abuse was **69% cocaine**, 25% opiates, 7% cannabis	**Dropout**: No sig difference between groups at 6 months (57% vs 46%, p=0.14) **Life satisfaction** (BQOL): Higher in CBT+MI group at 6 months (MD=0.58 [0.00 to 1.16], p=0.049	In Hunt 2019[2]

		Addiction Recovery (STAR)		**Quality of life** (BQOL): No sig difference between groups at 5 months (p=0.95) **Other outcomes**, skewed data: Global state (ASI)	
Morse 2006[3]	RCT 24 mo USA Community	(1) **I-ACT**: Integrated Assertive Community Treatment (2) **ACT**: Assertive Community Treatment Team only (3) **TAU**: referral to community agencies (mental health and substance abuse treatment)	N=196 homeless people with DSM-IV **serious mental illness** (48% schizophrenia, 19% schizoaffective disorder, 11% atypical psychotic disorder, 11% bipolar disorder, 9% major depression-recurrent disorder, 2% other) and **SUD. Cocaine most frequently used drug (34%)**	**Use disorder severity** (USS): skewed data **Days in stable housing** (mean): skewed data	In Hunt 2019[2]

BQOL
ASI
USS

Depression

Depression: Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				

Treatment retention	N/A	Meta-analysis: Hides 2019[4] (Not assessed)	<u>Integrated CBT for depression and substance use vs Twelve Step Facilitation:</u>
			• **No sig difference** in treatment retention (p=0.71) but significant heterogeneity (I^2=74%, p=0.05) in 2 RCTs, n=296.
			  ○ Brown 2006 (n=54, mixed SUD & MDD); Lydecker 2010 (n=166, mixed SUD & MDD)
			<u>Interpersonal Psychotherapy for Depression vs Other Therapy</u>
			• **No sig difference** in retention in 2 RCTs (n=64, p=0.98)
			  ○ Johnson 2012 (n=38, mixed SUDs & MDD, IPT-D vs Psychoeducation); Markowitz 2008 (n=26, AUD & dysthymia, IPT-D vs Brief Supportive Therapy)
			<u>Behavioral Therapy for Depression in Drug Dependence vs Control:</u>
			• **No sig difference** in 1 RCT (p=0.08)
			  ○ Carpenter 2008 (n=38 OUD)
				SUD and Major Depressive Disorder.
				
				Not stimulant specific.

		Meta-analysis: Hunt 2019[2] (Not assessed)	<u>Integrated models of care vs Standard care</u> • **No sig difference** in 3 studies, n=603 RR 1.09 (0.82 to 1.45). Low-quality evidence: Serious RoB, serious imprecision	SUD and severe mental illness

			○ Chandler 2006 (mixed SUD), Drake 1998a (mixed SUD), Essock 2006 (mixed SUD) <u>Non-integrated models of care vs Standard care</u> • **No sig difference** in 3 studies, n=134, RR 1.35 [0.83, 2.19] Very low-quality evidence: Very serious RoB, serious imprecision ○ Bond 1991a (mixed SUD); Bond 1991b (mixed SUD); Jerrell 1995b (mixed SUD)	Not stimulant specific. RoB=Risk of Bias
		Meta-analysis: Hesse 2009[5] (Not assessed)	<u>Psychological treatment for substance use and co-morbid depression vs. treatment for substance use alone</u> • **No sig difference** in dropout across 3 RCTs, n=150: (p=0.33) ○ Bowman 1996 (mixed SUD), Brown 2006a (alcohol), Daughters 2008 (mixed SUD)	SUD and anxiety or depression Not stimulant specific.
Depressive symptoms	N/A	Meta-analysis: Hides 2019[4] (Not assessed)	<u>Integrated CBT for depression and substance use vs Twelve Step Facilitation:</u> • **Twelve Step Facilitation** had lower depression scores (Hamilton Depression Rating Scale) at the end of treatment (24 wks) in 2 RCTs (n=212, MD=4.05 [1.43,6.66], p<0.01) ○ Brown 2006 (n=54, mixed SUD & MDD); Lydecker 2010 (n=166, mixed SUD & MDD) • **No sig difference** at 6- to 12-month follow-up in 2 RCTs (p=0.36) ○ Brown 2006 (n=54, mixed SUD & MDD); Lydecker 2010 (n=166, mixed SUD & MDD) <u>Interpersonal Psychotherapy for Depression (IPT-D) vs Other Therapy</u> • **IPT-D** had lower interviewer-rated depression (Hamilton Depression Rating Scale) at the end of treatment in 2 RCTs (SMD= -0.54 [-1.04, -0.04], p=0.03) ○ Johnson 2012 (n=38, mixed SUDs & MDD, IPT-D vs Psychoeducation); Markowitz 2008 (n=26, AUD & dysthymia, IPT-D vs Brief Supportive Therapy) • **No sig difference** at 3 mo follow-up in 1 RCT ○ Johnson 2012 (n=38, mixed SUDs & MDD, IPT-D vs Psychoeducation) <u>Behavioral Therapy for Depression in Drug Dependence vs Control:</u> • **No sig difference** at end of treatment in 1 RCT ○ Carpenter 2008 (n=38 OUD)	SUD and Major Depressive Disorder Not stimulant specific.
		Meta-analysis: Hesse 2009[5] (Not assessed)	<u>Psychological treatment for substance use and co-morbid depression vs. treatment for substance use alone</u> • **Integrated treatment** had lower HAM–D scores compared to SUD treatment alone in 4 RCTs (n=115, MD (95% CI) = -4.56 (-7.37, -1.74), p=0.001). Significant and moderate heterogeneity (I^2 = 0.61, p = 0.05). ○ Bowman 1996 (mixed SUD); Brown 1997 (alcohol); Daughters 2008 (mixed SUD); Markowitz 2008 (mixed SUD)	SUD and anxiety or depression Not stimulant specific.

			• **Integrated treatment** had lower SCL-90 or BDI scores compared to SUD treatment alone in 4 RCTs (n=155, SMD (95% CI) = -0.58 (-1.1, -0.06), p=0.03) Brown 1997 (alcohol); Brown 2006a (alcohol); Daughters 2008 (mixed SUD); Markowitz 2008 (mixed SUD)	
Substance use	N/A	Meta-analysis: Hides 2019[4] (Not assessed)	<u>Integrated CBT for depression and substance use vs Twelve Step Facilitation:</u> • **No sig difference** in post treatment (24 wks) self-reported substance use in 2 RCTs (n=296, p=0.28) o Brown 2006 (n=54, mixed SUD & MDD); Lydecker 2010 (n=166, mixed SUD & MDD) • **Integrated CBT** self-reported more days abstinent in prior 90 at 6- to 12-month follow-up in 2 RCTs (n=189, MD= 10.76, [3.1,18.42], p=0.01) o Brown 2006 (n=54, mixed SUD & MDD); Lydecker 2010 (n=166, mixed SUD & MDD) <u>Interpersonal Psychotherapy for Depression vs Other Therapy</u> • **No sig difference** in post treatment self-reported substance use in 2 RCTs o Johnson 2012 (n=38, mixed SUDs & MDD, IPT-D vs Psychoeducation); Markowitz 2008 (n=26, AUD & dysthymia, IPT-D vs Brief Supportive Therapy) • **No sig difference** at 3 mo follow-up in 1 RCT o Johnson 2012 (n=38, mixed SUDs & MDD, IPT-D vs Psychoeducation) <u>Behavioral Therapy for Depression in Drug Dependence vs Control:</u> • **No sig difference** in end of treatment cocaine use in 1 RCT o Carpenter 2008 (n=38 OUD)	SUD and Major Depressive Disorder Not stimulant specific
		Meta-analysis: Hunt 2019[2] (Not assessed)	<u>Integrated models of care versus standard care</u> • **No sig difference** in drug use in 1 study. Low-quality evidence: Serious RoB, serious imprecision o Drake 1998a (n=85, mixed SUD) <u>Non-integrated models of care vs Standard care</u> • **No sig difference** in 3 studies, n=134, RR 1.35 [0.83, 2.19] Very low-quality evidence: Very serious RoB, serious imprecision o Bond 1991a (mixed SUD); Bond 1991b (mixed SUD); Jerrell 1995b (mixed SUD)	SUD and severe mental illness Not stimulant specific
		Meta-analysis: Hesse 2009[5] (Not assessed)	<u>Psychological treatment for substance use and co-morbid depression vs. treatment for substance use alone</u> • **Integrated treatment** had more percent days abstinent in 4 RCTs, n=111: (MD (95% CI) = 13.75 (0.51, 26.99), p=0.04) o Brown 1997 (alcohol), Brown 2006a (alcohol), Markowitz 2008 (mixed SUD)	SUD and anxiety or depression Not stimulant specific.

Quality of life	N/A	Meta-analysis: Hunt 2019[2] (Not assessed)	Integrated models of care versus standard care • **No sig difference** in QOLI between Integrated models of care versus standard care across 2 studies, n=361 ○ Drake 1998a (n=85, mixed SUD); Essock 2006 (mixed SUD)	SUD and severe mental illness Not stimulant specific.

[i]: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

HAM–D

SCL-90

BDI

Depression: Individual Studies Table

Daley DC, Salloum IM, Zuckoff A, Kirisci L, Thase ME. Increasing treatment adherence among outpatients with depression and cocaine dependence: results of a pilot study. American Journal of Psychiatry 1998;155(11):1611–3.

Daughters, S. B. (2008). Effectiveness of a Brief Behavioral Treatment for Inner-City Illicit Drug Users With Elevated Depressive Symptoms: The Life Enhancement Treatment for Substance Use (LETS Act!). The Journal of Clinical Psychiatry, 69(1), 5538. https://doi.org/10.4088/JCP.v69n0116

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Brown 2006[6]	RCT 24 wks, 6-mo follow-up Dual diagnosis outpatient clinic for veterans	**(1) Integrated CBT:** Integrated manualized group CBT based on Cognitive-Behavioral Depression Treatment (Muñoz 1993) and Cognitive-Behavioral Coping Skills Training of Addiction (Kadden 1994). **(2) TSF:** Twelve Step Facilitation	N= 90 veterans with **substance** (alcohol, cannabis and/or stimulant) dependence and MDD (DSM-IV). 92% male, 74% white	**Treatment retention:** attended at least 8 of the 36 treatment sessions (77% vs 69%) **Substance use**: proportion of days abstinent out of the past 90 days at the end of treatment (24 wks) (84 vs 93, MD= -9[-23.97,5.97]) at 6- to 12-month follow-up (87 vs 72, MD= 15[-4.62,34.62]) **Depression** (HDRS, interviewer-rated): Depression in the past 7 days at the end of treatment (24 wks) (27.7 vs 23.2, MD= 4.5 [-4.14, 13.14]) at 6- to 12- month follow-up (25.9 vs 27.9, MD= -2 [-11.53, 7.53]	In Hides 2019[4] High RoB No ITT conducted Also in EtDT Co-Simultaneous
Kay-Lambkin 2010[7]	Non-randomized feasibility study 20 wks	(1) **Control group** (2) **Stepped care**: One-session integrated brief integration (BI), fixed integrated CBT/MI and stepped care, a healthcare	N=18 current **MA** users (at least once weekly) with moderate or greater depressive symptoms (Beck Depression Inventory II score >= 17) (56% men)	**Depression** (Beck Depression Inventory II): Participants receiving stepped-care intervention reported a 53% decrease in depression rating scores compared with a 48% decrease in the control group.	In Hellem 2015[8]

		model that supports starting with a less intensive approach to treatment and transitioning to more intensive therapy if indicated (Murphy, Lynch, Oslin, McKay, & TenHave, 2007),	**Depression not clinically diagnosed.**		
Lydecker 2010[9]	RCT 24 wks, 12-mo follow-up Dual diagnosis outpatient clinic for veterans	Same as Brown 2006	N=206 veterans with **substance** (alcohol, cannabis and/or stimulant) dependence and MDD (DSM-IV). Abstinence was a requirement at baseline. 92% male, 71% white	**Retention:** n.s.d. between groups (74% vs 88%) **Substance use**: proportion of days abstinent out of the past 90 days at the end of treatment (24 wks) (88 vs 90, MD= -2[-7.54,3.54]) at 6- to 12-month follow-up (85 vs 75, MD= 10[1.68,18.32]) **Depression** (HDRS, interviewer-rated): Depression in the past 7 days at the end of treatment (24 wks) (25 vs 21, MD= 4[1.26,6.74]). at 6- to 12- month follow-up (23 vs 21, MD= 2[-1.47,5.47])	In Hides 2019[4] High RoB Also in EtDT Co-Simultaneous
Wusthoff 2014[10]		Integrated treatment	substance use disorders co-occurring with anxiety and/or depression. Depression not clinically diagnosed.		In Hides 2019[4]

Depression: Non-systematic Reviews & Commentary

Source	Recommendation	Comments
Chiang 2019[11]	"Mindfulness-based relapse prevention (MBRP) methods have been shown to decrease craving and depressive symptoms for comorbid substance use in depressive disorders (Zemestani & Ottaviani, 2016)." Chiang 2019, p8[11]	

Depression: Other Resources

Source	Recommendation	Comments
	Substance Abuse and Mental Health Services Administration. (2020l). Substance use disorder treatment for people with co-occurring disorders. Treatment Improvement Protocol (TIP) Series 42. SAMHSA Publication No. PEP20-02-01-004. Substance Abuse and Mental Health Services Administration.	

Source	Recommendation	Comments
	Substance Abuse and Mental Health Services Administration. (2020n, August 19). Co-occurring disorders and other health conditions. https:// www.samhsa.gov/medication-assisted-treatment/ medications-counseling-related-conditions/ co-occurring-disorders	

Anxiety

Anxiety: Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
General	N/A	Meta-analysis: Hesse 2009[5] (Not assessed)	"For anxiety disorders, no meta-analysis could be conducted. However, based on this narrative review there is currently little evidence that offering non-somatic treatment for co-morbid anxiety disorders to patients with substance use disorders will yield any significant benefit; several studies report that outcomes for **integrated treatment** produced worse results than treatment that focused on substance use disorders alone [17,20]. One possible exception is treatment for co-morbid Obsessive-Compulsive Disorder [19], but this is based on a single, very small trial." (p. 7) Co-occurring Anxiety & AUD • 16. Bowen RC, D'Arcy C, Keegan D, Senthilselvan A: A controlled trial of cognitive behavioral treatment of panic in alcoholic inpatients with comorbid panic disorder. Addictive Behaviors 2000, 25(4):593-597. • 17. Randall CL, Thomas S, Thevos AK: Concurrent alcoholism and social anxiety disorder: a first step toward developing effective treatments. Alcohol Clin Exp Res 2001, 25(2):210-220. • 18. Schade A, Marquenie LA, van Balkom AJ, Koeter MW, de Beurs E, Brink W van den, van Dyck R: The effectiveness of anxiety treatment on alcohol-dependent patients with a comorbid phobic disorder: a randomized controlled trial. Alcohol Clin Exp Res 2005, 29(5):794-800. Co-occurring Anxiety & mixed alcohol and drug use disorder • 19. Fals-Stewart W, Schafer J: The treatment of substance abusers diagnosed with obsessive-compulsive disorder: an outcome study. Journal of Substance Abuse Treatment 1992, 9(4):365-370. • 20. Hien DA, Cohen LR, Miele GM, Litt LC, Capstick C: Promising treatments for women with comorbid PTSD and substance use disorders. American Journal of Psychiatry 2004, 161(8):1426-1432.	Integrated psychological treatment for substance use and co-morbid anxiety or depression vs. Treatment for substance use alone Not stimulant specific

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Anxiety: Individual Studies Table

Study	Design	Interventions	Participants	Outcomes	Comments
Courbasson & Nishikawa 2010[12]	Pre-post 10 wks Canada	**I-CBT**: Integrated group CBT	N=59 patients with comorbid social anxiety disorder (SAD) and **substance use disorder** (alcohol and/or drugs)	**Social anxiety**: Reduced **Negative affect**: Reduced **Positive affect**: No change **Unrealistic alcohol expectancies**: No change	Cited by Milosevic 2017[13]
Milosevic 2017[13]	Pre-post Canada **Outpatient anxiety clinic**	**I-CBT**: 12 group sessions of integrated CBT for comorbid mood, anxiety, and substance use disorders. Manualized.	N=68 adults with a current DSM-IV diagnosis of at least one depressive or anxiety disorder and alcohol or drug use disorder. **97% (28/29) had an anxiety disorder and AUD/SUD. 14% (4/29) had stimulant dependence/ abuse**, 18/29 alcohol, 12/29 cannabis, 2/29 opioid.	45 (66%) completed treatment, as defined by attendance of eight or more sessions. **Drug use**: No change **Alcohol use**: Reduced **Substance refusal self-efficacy**: Increased **Stress**: Reduced **Anxiety**: No change **Depression**: No change **Coping skills**: No change **Quality of life**: No change **Treatment satisfaction**: Participants reported being highly satisfied with treatment,	Lots of missing (demographic) data.
Wüsthoff 2014[10]	RCT 12 months Norway **Outpatient psychiatric clinics**	(1) **Integrated Treatment (IT):** Integrated treatment for mental and substance use disorder based on MI, CBT. (2) **TAU**	N=76 new adult patients with anxiety disorder and/or depression and substance disorder or abuse. **82% (62/76) with anxiety disorder, 40% (30/76) with drug use disorder.**	**Treatment completion**: No sig difference between groups (39/55 vs 17/21, p=0.37). **Drug use** (DUDIT): No sig difference between groups in reduction. **Alcohol use** (AUDIT): No sig difference between groups in reduction. **Psychiatric symptoms** (SCL-90r): No sig reduction **Motivation for substance use treatment** (SATS-r): IT group had a greater increase after 12 months compared to TAU (β=1.76, 95% CI [0.08, 3.44], p = 0.043).	ITT analysis

URICA = University of Rhode Island change assessment

Anxiety: Other Resources

Source	Recommendation	Comments
	Substance Abuse and Mental Health Services Administration. (2020l). Substance use disorder treatment for people with co-occurring disorders. Treatment Improvement Protocol (TIP) Series 42. SAMHSA Publication No. PEP20-02-01-004. Substance Abuse and Mental Health Services Administration.	
	Substance Abuse and Mental Health Services Administration. (2020n, August 19). Co-occurring disorders and other health conditions. https:// www.samhsa.gov/medication-assisted-treatment/ medications-counseling-related-conditions/ co-occurring-disorders	

PTSD

PTSD: Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				

Treatment completion	Low	Meta-analysis: Roberts 2016[14] (Not assessed)	<u>Trauma-focused therapy plus adjunctive SUD treatment vs TAU/minimal intervention:</u>
			• **Trauma-focused therapy plus adjunctive SUD treatment** had fewer participants complete (3 studies, n=316, RR= 0.78 [0.64, 0.96], p=0.02; I^2=41%, p=0.18) Low-quality evidence.
			  ○ Coffey 2006 (n=43 AUD & PTSD, Imaginal exposure vs Control); Coffey unpublished (n=222 AUD & PTSD, Trauma-focused exposure therapy vs Control); Foa 2013 (n=657 w/ AUD & PTSD, Prolonged exposure + Counseling vs Counseling)
			
			<u>Non-trauma-focused Integrated therapy vs TAU/minimal intervention:</u>
			• **No sig difference** (2 studies, n=381, p=0.36; I^2=10%, p=0.29). Low-quality evidence
			  ○ Hien 2009 (n=1963 women w/ trauma [80% PTSD] & SUD, Seeking Safety vs Women's Health Education); Norman unpublished (n=78 women w/ AUD & PTSD, Seeking Safety vs 12-Step)
			
			<u>Trauma-focused Integrated therapy vs SUD treatment alone:</u>
			• **No sig difference** (1 study; n=62). Low-quality evidence.
			  ○ Sannibale 2013 (n=154 w/ AUD & PTSD, Integrated CBT vs CBT for AUD)
			
			<u>Non-trauma-focused Integrated therapy vs SUD treatment alone:</u>
				Cochrane Review of psychological therapies for PTSD and SUD
				
				Not stimulant specific

			• **No sig difference** (2 studies; n=128, p=0.50; I^2=0%, p=0.55). Very low-quality evidence. o Hien 2004 (n=207 women w/ SUD & PTSD, Seeking Safety + TAU vs Relapse Prevention + TAU vs TAU); McGovern 2011 (n=77 w/ PTSD & SUD, Integrated CBT vs SUD tx)	
Important Outcomes				
Substance use	N/A	Meta-analysis: Roberts 2016[14] (Not assessed)	<u>Trauma-focused therapy + adjunctive SUD intervention vs TAU/minimal intervention</u> • **No sig difference** between in drug/alcohol use at treatment end (3 studies, n=388, SMD= -0.13 [-0.41, 0.15], p=0.35; I^2=45%, p=0.16). Very low-quality evidence o Coffey unpublished (n=222 w/ AUD & PTSD, Trauma-focused exposure therapy vs Control); Foa 2013 (n=657 w/ AUD & PTSD, Prolonged exposure + Counseling vs Counseling); Mills 2012 (n=334 w/ SUD & PTSD, Integrated COPE vs TAU) <u>Trauma-focused therapy + adjunctive SUD vs TAU/minimal intervention</u> • **Trauma-focused therapy + adjunctive SUD** had a small benefit at 5 to 7-month follow-up (3 studies, n=388, SMD= -0.28 [-0.48, -0.07], p=0.01; I^2=0%, p=0.88). Low-quality evidence. o Coffey unpublished (n=222 w/ AUD & PTSD, Trauma-focused exposure therapy vs Control); Foa 2013 (n=657 w/ AUD & PTSD, Prolonged exposure + Counseling vs Counseling); Mills 2012 (n=334 w/ SUD & PTSD, Integrated COPE vs TAU) <u>Non-trauma-focused integrated therapy vs TAU/minimal intervention</u> • **No sig difference** at treatment end (3 studies, n=464, p=0.15; I^2=79%, p=0.01). Very low-quality evidence. o Boden 2012 (n=125 male veterans w/ [91% PTSD] & SUD, Seeking Safety vs TAU); Hien 2009 (n=1963 women w/ trauma [80% PTSD] & SUD, Seeking Safety vs Women's Health Education); Norman unpublished (n=78 women w/ AUD & PTSD, Seeking Safety vs 12-Step) • "A post-hoc analysis for full dose of a widely established group therapy called Seeking Safety showed reduced drug/alcohol use post-treatment (SMD -0.67; 95% CI -1.14 to -0.19; 2 studies; n = 111), but not at subsequent follow-ups" (p. 2). <u>Trauma-focused integrated therapy vs SUD treatment alone:</u> • **No sig difference** at treatment end (1 study; n=46; low-quality evidence) o Sannibale 2013 (n=154 w/ AUD & PTSD, Integrated CBT vs CBT for AUD) <u>Non-trauma-focused integrated therapy vs SUD therapy</u>	Cochrane Review of psychological therapies for PTSD and SUD Not stimulant specific.

			• **No sig difference** at treatment end (2 studies, n=128, p=0.22; I^2=0%, p=0.60). Low-quality evidence. o Hien 2004 (n=207 women w/ SUD & PTSD, Seeking Safety + TAU vs Relapse Prevention + TAU vs TAU); McGovern 2011 (n=77 w/ PTSD & SUD, Integrated CBT vs SUD tx)	
SUD symptoms	N/A	Meta-analysis: Torchalla 2012[15] (Not assessed)	**Integrated SUD & PTSD treatment** programs for individuals with concurrent substance use disorders and trauma experiences showed a significant change in SUD symptoms from baseline to longest follow-up (k = 16, d = 0.60 [0.42, 0.78], p <0.001). • Brady 2001 (n=39 PTSD & CoUD); Donovan 2001; Frisman 2008; Hien 2004; Hien 2009; McFall 2005; McFall 2006; McGovern 2009; Morrissey 2005; Najavits 1998; Najavits 2005; Najavits 2006; Sacks 2008; Triffleman 2000; Zlotnick 2003; Zlotnick 2009 (n=92 incarcerated women w/ [83% PTSD] & SUD [94% CoUD], Seeking Safety + TAU vs TAU) <u>Integrated SUD & PTSD treatment vs Non-integrated TAU/control</u> • **No sign difference** in SUD symptoms at longest follow-up (k = 9, d = 0.10 [−0.01, 0.21], p=0.08). o Frisman 2008; Hien 2004; Hien 2009; McFall 2005; Morrissey 2005; Najavits 2006; Sacks 2008; Triffleman 2000; Zlotnick 2009 (n=92 incarcerated women w/ [83% PTSD] & SUD [94% CoUD], Seeking Safety + TAU vs TAU)	Integrated treatment programs for individuals with concurrent SUD and trauma experiences

PTSD symptoms	N/A	Meta-analysis: Roberts 2016[14]
		(Not assessed)
			<u>Trauma-focused integrated therapy vs SUD tx alone:</u>
			• **No sig difference** (1 study, n=46) Low-quality evidence
			  o Sannibale 2013 (n=154 w/ AUD & PTSD, Integrated CBT vs CBT for AUD)
			
			<u>Non-trauma-focused therapy for PTSD & SUD or PTSD alone vs SUD tx alone:</u>
			• **No sig difference** (2 studies, n=128, p=0.62; I^2=87%, p<0.001). Very low-quality evidence
			  o Hien 2004 (n=207 women w/ SUD & PTSD, Seeking Safety + TAU vs Relapse Prevention + TAU vs TAU); McGovern 2011 (n=77 w/ PTSD & SUD, Integrated CBT vs SUD tx)
			
			<u>Trauma-focused therapy + adjunctive SUD intervention vs TAU/minimal intervention:</u>
			• **Trauma-focused therapy + adjunctive SUD** was more effective at the end of intervention (4 studies, n=405, SMD= -0.41 [-0.72, -0.10], p=0.01; I^2=49%, p=0.11). Very low-quality evidence
			  o Coffey 2006 (n=43 w/ AUD & PTSD, Imaginal exposure vs Control); Coffey unpublished (n=222 AUD & PTSD, Trauma-focused exposure therapy vs Control); Foa 2013 (n=657 w/ AUD & PTSD, Prolonged exposure +
				Cochrane Review of psychological therapies for PTSD and SUD
				
				Not stimulant specific.

			Counseling vs Counseling); Mills 2012 (n=334 w/ SUD & PTSD, Integrated COPE vs TAU) • **Trauma-focused therapy + adjunctive SUD** was more effective at 5 to 7 months' follow-up (3 studies, n=388, SMD= -0.34 [-0.58, -0.1], p=0.01; I^2=26%, p=0.26) o Coffey unpublished (n=222 w/ AUD & PTSD, Trauma-focused exposure therapy vs Control); Foa 2013 (n=657 w/ AUD & PTSD, Prolonged exposure + Counseling vs Counseling); Mills 2012 (n=334 w/ SUD & PTSD, Integrated COPE vs TAU) Non-trauma-focused therapy for PTSD & SUD or PTSD alone vs TAU/minimal intervention • **No sig difference** at end-of-treatment (5 studies, n=557, p=0.85; I^2=0%, p=0.85). Low-quality evidence o Mueser 2008 (n=280 w/ [41% SUD] & PTSD & SMI, CBT for PTSD vs TAU); Boden 2012 (n=125 male veterans w/ [91% PTSD] & SUD, Seeking Safety vs TAU); Hien 2009 (n=1963 women w/ trauma [80% PTSD] & SUD, Seeking Safety vs Women's Health Education); Norman unpublished (n=78 women w/ AUD & PTSD, Seeking Safety vs 12-Step); Zlotnick 2009 (n=92 incarcerated women w/ [83% PTSD] & SUD [94% CoUD], Seeking Safety + TAU vs TAU)	
		Meta-analysis: Torchalla 2012[15] (Not assessed)	**Integrated SUD & PTSD treatment** programs for individuals with concurrent substance use disorders and trauma experiences showed a significant change in PTSD symptoms from baseline to the longest available follow-up (k=15, d=0.88 [0.66, 0.09], p < 0.001). • Brady 2001 (n=39 PTSD & CoUD), Donovan 2001; Frisman 2008; Hien 2004; Hien 2009; McGovern 2009; Morrissey 2005; Najavits 1998; Najavits 2005; Najavits 2006; Sacks 2008; Triffleman 2000; Weller 2005; Zlotnick 2003; Zlotnick 2009 (n=92 incarcerated women [83% PTSD] & SUD [94% CoUD], Seeking Safety + TAU vs TAU) Integrated SUD & PTSD treatment vs Non-integrated TAU/control: • **No sig difference** in PTSD symptoms at longest follow-up (k=10, d=0.08 [−0.03, 0.19], p = 0.15). o Frisman 2008; Hien 2004; Hien 2009; Morrissey 2005; Najavits 2006; Sacks 2008; Triffleman 2000; Zlotnick 2009 (n=92 incarcerated women [83% PTSD] & SUD [94% CoUD], Seeking Safety + TAU vs TAU)	Integrated treatment programs for individuals with concurrent SUD and trauma experiences
Adverse events	N/A	Meta-analysis: Roberts 2016[14] (Not assessed)	Trauma-focused Integrated therapy and Control therapy • **No sig difference** in number of adverse events (2 studies, n=268, p=0.63; I^2=0%, p=0.43) o Foa 2013 (n=657 AUD & PTSD, Prolonged exposure + Counseling vs Counseling); Mills 2012 (n=334 SUD & PTSD, Integrated COPE vs TAU)	Cochrane Review of psychological therapies for PTSD and SUD

				Not stimulant specific.

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

†Evidence drawn from people with SUD and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically

COPE = Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure

PTSD: Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Brady 2001[16]	Uncontrolled 6 mo follow-up	Concurrent treatment of PTSD and cocaine dependence	N=39 adults with PTSD and **cocaine** dependence	**SUD symptoms**: Improved over time **PTSD symptoms**: No difference **Mental health symptoms**: Improved over time	In Torchalla 2012[15]
Zlotnick 2009[17]	RCT 6-8 wks USA Controlled setting	(1) Seeking Safety + TAU: Group-based integrated treatment for trauma/ PTSD and substance abuse. (2) TAU	N=49 incarcerated women with PTSD and polydrug use. 93.9% met lifetime criteria for **cocaine** dependence	**SUD:** No sig difference between groups **PTSD remission**: No sig difference between groups **Psychopathology**: No sig difference between groups	In Roberts 2016[14]

PTSD: Other Resources

Resources
SAMHSA's TIP 57, Trauma-Informed Care in Behavioral Health Services (https:// store.samhsa.gov/product/TIP-57-TraumaTreatment for Stimulant Use Disorders Informed-Care-in-Behavioral-Health-Services/ SMA14-4816).
SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach (https://store.samhsa. gov/product/SMA14-4884): This manual provides a working concept of trauma and key principles of a trauma-informed treatment approach that can be used by behavioral health workers and an array of service systems. It also suggests methods for implementing a trauma-informed approach.
U.S. Department of Veterans Affairs (VA), National Center for PTSD (https://www.ptsd. va.gov/professional/index.asp): VA offers training materials, information, and tools to assess and treat trauma-related disorders. This website contains links to continuing education on posttraumatic stress disorder (PTSD), free training in prolonged exposure therapy for providers who treat veterans, and links to VA benefts.

Trauma Informed Oregon's tip sheet, Trauma Informed Urine Drug Screenings (https://traumainformedoregon.org/ wp-content/uploads/2019/05/Urine-Drug-Screentip-sheet.pdf).
Substance Abuse and Mental Health Services Administration. (2020l). Substance use disorder treatment for people with co-occurring disorders. Treatment Improvement Protocol (TIP) Series 42. SAMHSA Publication No. PEP20-02-01-004. Substance Abuse and Mental Health Services Administration.
Substance Abuse and Mental Health Services Administration. (2020n, August 19). Co-occurring disorders and other health conditions. https:// www.samhsa.gov/medication-assisted-treatment/ medications-counseling-related-conditions/ co-occurring-disorders

ADHD

ADHD: Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Van Emmerik-van Oortmerssen 2019[18]	RCT 2-month follow-up Netherlands Outpatient	(1) **Integrated CBT for SUD & ADHD**: 15 individual sessions of motivational therapy, coping skills training and relapse prevention for SUD, and training of planning skills, problem-solving skills and dealing with emotions for ADHD. (2) **CBT for SUD**: 10 individual SUD treatment sessions only	N=119 treatment-seeking adults with ADHD and SUD other than nicotine (primary substance of abuse stimulants, n=28, 23.5%). 5 participants already on ADHD medication at the start of the trial were asked to maintain dose, but patients did not start medication during the trial. Patients with (a history of) severe neurological (eg, dementia, Parkinson's disease), severe psychiatric disorders (eg, psychosis, bipolar disorder), borderline personality disorder were excluded	**ADHD symptom severity** (ARS): Integrated CBT had lower scores at the end of treatment (M[sd] 28.1 [9.0] vs 31.5 [11.4], F=4.739, df = 1, 282, p=0.030; d=0.34). n.s.d. at 2-month follow-up (p=0.076). **Other outcomes**: n.s.d. in substance use (TLFB self-report), Depressive symptoms (BDI), Anxiety symptoms (BAI), Quality of life (BQ-5D)	

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Studies of integrated behavioral treatment of SUD and co-occurring mental health disorders are heterogeneous in design, target population and outcomes of evaluation. Interventions are not specific to StUD populations. Depression: There is no MA/SR evidence specific to stimulant use disorder populations. There is evidence from 3 meta-analyses of broader SUD studies suggesting that integrated treatment for SUD and depression may reduce depressive symptoms. Anxiety: Limited studies of integrated CBT interventions suggest minimal change in SUD/anxiety outcomes. Some evidence suggested worse outcomes (?). PTSD: Studies of integrated trauma focused therapy suggest limited benefit in SUD and PTSD outcomes.	While the evidence is not stimulant-specific, it is reasonable to assume that data from SUD studies will apply to patients with StUD. In the view of the CGC, the benefits of addressing both the target SUD as well as other clinical conditions are potentially large.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence from existing studies does not suggest significant adverse effects or differences in dropout, although some studies of integrated models (eg PSTD) were associated with reduced treatment completion.		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Heterogeneous studies with limited evidence		☐ No evidence ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒Varies

***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Participation in integrated treatment is likely more efficient and cost effective for patients than parallel or sequential treatment models.		☐ No ☐ Probably no ☐ Uncertain ☒Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
Due to heterogeneity in COD populations, it may not always be feasible to implement integrated behavioral treatment interventions that have been developed for specific CODs, particularly for disorders that are less prevalent. Clinician training and resources may limit feasibility.		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Studies on integrated behavioral treatment approaches are limited and heterogeneous in design, target population, and outcomes of evaluation. Studies are not specific to StUD and include approaches that target mixed SUDs and co-occurring depression, anxiety disorders, or PTSD; findings are mixed, but some benefits in reduction of substance use or psychiatric symptoms likely apply to StUD populations. Integrating treatment of SUD and co-occurring mental health disorders is likely more convenient and cost-effective for patients than parallel or sequential treatment models, with benefits most likely largely outweighing risks or harms.

Subgroup Considerations

Some approaches are developed for populations with specific disorders, and thus less generalizable.

Implementation Considerations

Implementation requires clinician skill and training for integrated and manualized treatment approaches.

Research Priorities

Additional research on integrated behavioral treatment approaches for StUD populations is warranted.

References

1. Bellack AS, Bennett ME, Gearon JS, Brown CH, Yang Y. A Randomized Clinical Trial of a New Behavioral Treatment for Drug Abuse in People With Severe and Persistent Mental Illness. *Arch Gen Psychiatry*. 2006;63(4):426. doi:10.1001/archpsyc.63.4.426
2. Hunt GE, Siegfried N, Morley K, Brooke-Sumner C, Cleary M. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Schizophrenia Group, ed. *Cochrane Database Syst Rev*. Published online December 12, 2019. doi:10/ggfhzg
3. Morse GA, Calsyn RJ, Dean Klinkenberg W, et al. Treating Homeless Clients with Severe Mental Illness and Substance Use Disorders: Costs and Outcomes. *Community Ment Health J*. 2006;42(4):377-404. doi:10.1007/s10597-006-9050-y
4. Hides L, Quinn C, Stoyanov S, Kavanagh D, Baker A. Psychological interventions for co-occurring depression and substance use disorders. *Cochrane Database Syst Rev*. 2019;2019(11). doi:10.1002/14651858.CD009501.pub2
5. Hesse M. Integrated psychological treatment for substance use and co-morbid anxiety or depression vs. treatment for substance use alone. A systematic review of the published literature. *BMC Psychiatry*. 2009;9:6. doi:10.1186/1471-244X-9-6
6. Brown SA, Glasner-Edwards SV, Tate SR, McQuaid JR, Chalekian J, Granholm E. Integrated Cognitive Behavioral Therapy Versus Twelve-Step Facilitation Therapy for Substance-Dependent Adults with Depressive Disorders. *J Psychoactive Drugs*. 2006;38(4):449-460. doi:10.1080/02791072.2006.10400584
7. Kay-Lambkin FJ, Baker AL, Mcketin R, Lee N. Stepping through treatment: Reflections on an adaptive treatment strategy among methamphetamine users with depression. *Drug Alcohol Rev*. 2010;29(5):475-482. doi:10.1111/j.1465-3362.2010.00203.x
8. Hellem TL, Lundberg KJ, Renshaw PF. A review of treatment options for co-occurring methamphetamine use disorders and depression. *J Addict Nurs*. 2015;26(1):14-23; quiz E1. doi:10.1097/JAN.0000000000000058
9. Lydecker KP, Tate SR, Cummins KM, McQuaid J, Granholm E, Brown SA. Clinical outcomes of an integrated treatment for depression and substance use disorders. *Psychol Addict Behav*. 2010;24(3):453-465. doi:10.1037/a0019943
10. Wüsthoff LE, Waal H, Gråwe RW. The effectiveness of integrated treatment in patients with substance use disorders co-occurring with anxiety and/or depression - a group randomized trial. *BMC Psychiatry*. 2014;14(1):67. doi:10.1186/1471-244X-14-67
11. Chiang M, Lombardi D, Du J, et al. Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options. *Hum Psychopharmacol*. 2019;34(5):e2710. doi:10.1002/hup.2710
12. Courbasson CM, Nishikawa Y. Cognitive Behavioral Group Therapy for Patients with Co-Existing Social Anxiety Disorder and Substance Use Disorders: A Pilot Study. *Cogn Ther Res*. 2010;34(1):82-91. doi:10.1007/s10608-008-9216-8
13. Milosevic I, Chudzik SM, Boyd S, McCabe RE. Evaluation of an integrated group cognitive-behavioral treatment for comorbid mood, anxiety, and substance use disorders: A pilot study. *J Anxiety Disord*. 2017;46:85-100. doi:10.1016/j.janxdis.2016.08.002
14. Roberts NP, Roberts PA, Jones N, Bisson JI. Psychological therapies for post-traumatic stress disorder and comorbid substance use disorder. *Cochrane Database Syst Rev*. 2016;(4). doi:10.1002/14651858.CD010204.pub2
15. Torchalla I, Nosen L, Rostam H, Allen P. Integrated treatment programs for individuals with concurrent substance use disorders and trauma experiences: a systematic review and meta-analysis. *J Subst Abuse Treat*. 2012;42(1):65-77. doi:10.1016/j.jsat.2011.09.001
16. Brady KT, Dansky BS, Back SE, Foa EB, Carroll KM. Exposure therapy in the treatment of PTSD among cocaine-dependent individuals: preliminary findings. *J Subst Abuse Treat*. 2001;21(1):47-54. doi:10.1016/s0740-5472(01)00182-9
17. Zlotnick C, Johnson J, Najavits LM. Randomized controlled pilot study of cognitive-behavioral therapy in a sample of incarcerated women with substance use disorder and PTSD. *Behav Ther*. 2009;40(4):325-336. doi:10.1016/j.beth.2008.09.004
18. van Emmerik-van Oortmerssen K, Vedel E, Kramer FJ, et al. Integrated cognitive behavioral therapy for ADHD in adult substance use disorder patients: Results of a randomized clinical trial. *Drug Alcohol Depend*. 2019;197:28-36. doi:10.1016/j.drugalcdep.2018.12.023

Table 18. Psychosis

Recommendation: Symptoms of psychosis or mania should be treated with indicated pharmacotherapy.

Clinical Question Summary

Clinical Question	1. Should clinicians use pharmacotherapy to treat psychosis or mania if it is unclear whether the condition is pre-existing or stimulant-induced? 2. What contextual factors and implementation strategies may influence the decision to use pharmacotherapy? 3. What are the most effective and appropriate interventions for treating psychosis in patients with stimulant use disorder?
Population	Patients with stimulant disorder experiencing psychosis
Intervention	Pharmacotherapy for psychosis
Comparison	TAU
Main Outcomes	Treatment retention, Stimulant use, Substance use, Adverse events, Psychotic symptoms, SUD symptom severity
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Treating stimulant psychosis vs treating StUD in underlying psychosis Notes: • "Aripiprazole is indicated for treatment of psychotic symptoms in schizophrenia [30]… Positive symptoms in schizophrenia are hypothesized to result from excess subcortical dopamine release [30], whereas disturbed mesolimbic dopamine neurotransmission is believed to play a major role in psychostimulant dependence [31]. It is possible that aripiprazole counteracts the high dopamine levels found during the bingeing periods of the dependence cycle that causes psychotic symptoms, and thus exert its effect on those symptoms." (Sulaiman 2013, p. 6)[1] Psychosis/Psychotic Disorder • "Studies of putative risk factors have examined psychological, genetic, and drug use variables, each of which has been shown to contribute to the variability in psychotic symptom onset and duration." (Glasner-Edwards & Mooney 2014, p. 5)[2] • MA use has a dose-response relationship with the exacerbation of positive psychotic, affective and psychomotor symptoms, but not negative psychotic symptoms (McKetin 2016)[3]. • "Patients who previously experienced methamphetamine-induced psychoses are at a higher risk of developing psychoses again. But also a history of schizophrenia and schizotypal personality traits are associated with a higher probability of psychotic symptoms in amphetamine users [239]." (Braunwarth 2016, p88)[4] • Hajebi et al 2016 found "The MAP group was related to the highest rates of suicide attempts and hospital readmissions, demonstrating a worse expected outcome for MAP compared with other psychotic disorders. Worse outcome was thought to be produced by frequent relapses and other drug-related comorbidity in the MAP population." (Chiang 2019, p4)[5] • "Acute stimulant-induced psychosis is directly related to the amount of substance used and lack of sleep of a specific binge." (SAMHSA 2021, p. 63)[6]. • ATS use was associated with an increased risk of psychosis compared to no ATS use (OR 2.0 [1.3 – 3.3]) in one review (McKetin 2019)[7]. No use could include the use of other substances. Farrell 2019[8] identified this as Level E evidence (findings of cross-sectional associations among non-representative samples of drug users, case series suggesting outcomes)

	Other • "For MA use, people appear more likely to have non-substance-induced, preexisting lifetime depressive, anxiety, or psychotic disorders than to have MA-induced depressive, anxiety, or psychotic disorders (Sal0 2011)[9] (SAMHSA, 2021, p. 68)[6]
Abbreviations	**ARDA:** Amphetamine, related derivatives, and analogues, **ATS:** Amphetamine-type stimulant, **AUD**: Alcohol use disorder, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **OUD**: Opioid Use Disorder, **RCT**: Randomized Control Trial, **SMI**: Severe mental illness, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Primary or Persistent Psychosis

Background

- McKetin 2017[10] and McKetin 2012[11]: In 330 participants with MaUD, transient MA-related psychosis (symptoms only when using MA) was associated with persecutory delusions and tactile hallucinations. Persistent MA-related psychosis (symptoms both when using and abstaining from MA) was additionally associated with delusions of reference, thought interference and complex auditory, visual, olfactory and tactile hallucinations. Primary psychotic disorder (DSM-IV criteria for lifetime schizophrenia or mania) was additionally associated with delusions of thought projection and passivity.
- Among 102 patients admitted to a psychiatric hospital, drug treatment center, or psychiatric outpatient clinic diagnosed with functional psychotic disorder or MA-associated psychosis (MAP); in general, delusions were more common in schizophrenia spectrum disorders, and hallucinations were more common in MAP (Shelly 2016)[12].
- Among 125 adults with a lifetime diagnosis of CoUD, lifetime substance-induced psychotic disorder (SIPD) was significantly associated with visual hallucinations, while lifetime independent psychotic disorder (IPD) was significantly associated with grandiose delusions and disorganized speech (Vergara-Moragues 2016)[13].
- In a Chinese case-control study, 106 adults seeking treatment for psychotic symptoms, patients with a history of persistent MA-associated psychosis was associated with visual hallucinations and somatic or tactile hallucinations compared to patients with schizophrenia spectrum disorders (Wang 2016)[14].

Psychosis: Systematic Reviews and Meta-Analyses

Antipsychotics

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Psychotic symptoms	Moderate	Meta-analysis: Srisurapanont 2021 [15] (High)	**Author conclusion:** "This analysis suggests that olanzapine or quetiapine may be a preferred antipsychotic for [MA psychosis], although the evidence for this was rated low-quality due to the high risk of bias or indirectness/intransitivity." (p. 1) Network meta-analysis comparing reduction in overall psychotic symptoms measured with validated scales (BPRS, SAPS, PANSS) of 6 antipsychotics for MA psychosis across 6 RCTs of 389 patients.	ATS- or MA-associated

			No heterogeneity (I^2 = 0 %). Visual inspection of funnel plots suggests "very low" level of publication bias. Significant differences: • **Olanzapine** > risperidone (SMD = -1.09, 95% CI -1.89 to -0.28) Quality of evidence: Low • **Quetiapine** > risperidone (SMD = -0.86, 95% CI -1.61 to -0.11) Quality of evidence: Low • Aripiprazole < **Olanzapine** (SMD = 1.36, 95% CI 0.46–2.26) Quality of evidence: Low • Aripiprazole < **Quetiapine** (SMD = 1.13, 95% CI 0.28–1.98) Quality of evidence: Low • Aripiprazole < **Haloperidol** (SMD = 0.87, 95% CI 0.14–1.60) Quality of evidence: Low • Aripiprazole < **Paliperidone extended-release** (SMD = 0.60, 95% CI 0.06–1.14) Quality of evidence: Low Included studies: • Farnia 2014 (n=53 ATS-induced, 6 wks Aripiprazole 15 mg/d vs Risperidone 4 mg/d); Leelahanaj 2005 (n=58 ATS-induced, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d); Samiei 2016 (n=44 MA-associated open-label, 3 wks Haloperidol 5-20 mg/d vs Risperidone 2-8 mg/d); Verachai 2014 (n=80 MA-induced, 4 wks Quetiapine 100-300 mg/d vs Haloperidol 2-6 mg/d); Wang 2016b (n=43 MA-associated open-label, 25 days Aripiprazole 5-15 mg/d vs Risperidone 4-6 mg/d); Wang 2020 (n=120 MA-associated, 25 days Risperidone 3-6 mg/d vs Paliperidone ER 3-9 mg/d)	
		Systematic review: Siefried 2020[16] (High)	**Aripiprazole > Placebo** in psychotic symptom control for MaUD with a history of psychotic symptoms in 1 RCT • Sulaiman 2013 (n=37 MaUD h/o psychosis, 8 wks aripiprazole 5-10 mg/d vs placebo)	MaUD h/o psychosis
		Meta-analysis: Indave 2016[17] (Not assessed)	**Haloperidol > Olanzapine** in reducing psychotic symptoms (PANSS) in 1 RCT (MD -6.10, 95% CI -10.93 to -1.27) • Smelson 2006b (n=31 CoUD & schizophrenia 6 wks)	Not intoxicated patients
		Systematic review: Richards 2015[18] (Moderate)	"For control of agitation and psychosis from ARDA, butyrophenones and later-generation antipsychotics are a reasonable choice, with the understanding extrapyramidal side effects may occur" (Richards, 2015, p. 10). • Conclusions based on 6 RCTs, 23 case series and reports on the use of antipsychotics to treat ARDA-associated agitation and psychosis. Included RCTs: • Leelahanaj 2005 (n=58 ATS psychosis 4 wks) Equivalent Olanzapine (5-20 mg/d) vs Haloperidol (5-20 mg/d); Sulaiman 2013 (n=37 MaUD h/o psychosis 8 wks) Aripiprazole (5-10 mg/d) > Placebo; Farnia 2014 (n=45 ATS 6 wks) Risperidone (4 mg/d) > Aripiprazole (15 mg); Verachai 2014 (n=80 MA 4 wks) Equivalent Quetiapine (100 mg/d) vs Haloperidol (2 mg/d); Richards 1997 (n=146 MA 60 mins) Droperidol > Lorazepam Prospective controlled • Angrist 2001 (n=18 ATS haloperidol)	ATS -associated agitation and psychosis

Dropout	N/A	Meta-analysis: Srisurapanont 2021[15] (High)	**No significant difference** was found; moderate heterogeneity (I^2 = 72.5 %). "Undetermined" level of publication bias based on visual inspection of the funnel plots. Network meta-analysis comparing dropout rates of 5 antipsychotics against risperidone for ATS-induced psychosis across 6 RCTs • Farnia 2014 (n=53, 6 wks Aripiprazole 15 mg/d vs Risperidone 4 mg/d); Leelahanaj 2005 (n=58, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d); Samiei 2016 (n=44 open-label, 3 wks Haloperidol 5-20 mg/d vs Risperidone 2-8 mg/d); Verachai 2014 (n=80, 4 wks Quetiapine 100-300 mg/d vs Haloperidol 2-6 mg/d); Wang 2016b (n=43 open-label, 25 days Aripiprazole 5-15 mg/d vs Risperidone 4-6 mg/d); Wang 2020 (n=120m, 25 days Risperidone 3-6 mg/d vs Paliperidone ER 3-9 mg/d)	ATS- or MA-associated
		Systematic review: Siefried 2020[16] (High)	**Aripiprazole > Placebo** in retention for MaUD with a history of psychotic symptoms in 1 RCT • Sulaiman 2013 (n=37 MaUD h/o psychosis, 8 wks aripiprazole 5-10 mg/d vs placebo)	MaUD h/o psychosis
Dropout due to adverse events	N/A	Meta-analysis: Chan 2019a[19] (Moderate); Chan 2020[20] (Moderate-high)	**No significant difference** between aripiprazole and placebo in dropout due to adverse events in 1 high RoB RCT • Moran 2017 (n=18 CoUD & OUD in MMT, 12 wks 15 mg/d aripiprazole vs placebo) Risk of Bias: High	CoUD, not intoxicated patients
		Meta-analysis: Chan 2019b[21] (Not assessed)	**No significant difference** between aripiprazole and placebo in dropout due to adverse events in 2 RCTs of in 143 patients with amphetamine or methamphetamine use disorder. • Coffin, 2012 10 mg/day 12 weeks; Tiihonen, 2007, 15 mg/day 20 weeks	ATS, not intoxicated patients
		Meta-analysis: Kishi 2013[22] (Not rated)	**Placebo > Antipsychotics** in medication side effects (8 studies, n= 395, RR (95% CI) = 4.48 (1.85, 10.85), p= 0.0009) • Coffin 2012 (Aripiprazole 10 mg/d 12 weeks); Newton 2008 (Aripiprazole 15 mg/d, 2 weeks); Sulaiman 2013 (Aripiprazole 5-10 mg/d, 8 weeks); Tiihonen 2007 (Aripiprazole 15 mg/d 20 weeks); Winhusen 2007a (Reserpine 0.5 mg/d, 12 weeks); Levin 1999 (Risperidone mean 2.1 mg/d 12 weeks); Loebl 2008 (Risperidone long-acting 25 mg IM every other week, 12 weeks); Smelson 2004 (Risperidone 1 mg/d 2 weeks). **Placebo > Ariprazole** in dropouts due to medication side effects: 4 studies, n= 196, RR (95% CI) = 4.64 (1.56, 13.86), p= 0.006. • Coffin (2012), Newton (2008), Sulaiman (2013, aripiprazole 5-10 mg/day 8 weeks), Tiihonen (2007) **No significant difference** between reserpine and placebo. • Winhusen (2007a), Levin (1999), Loebl (2008), Smelson (2004)	Not intoxicated patients. Includes studies of amphetamine, cocaine, and methamphetamine use disorder populations.

Important Outcomes				
Adverse events	N/A	Systematic review: Richards 2016[23] (Low)	**3 adverse events out of 168 patients (1.8%)** treated with antipsychotics for acute cocaine toxicity**:** One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).	Acute cocaine toxicity
		Systematic review: Richards 2015[18] (Moderate)	**5 adverse events out of 287 patients (1.7%)** receiving antipsychotics for ATS toxicity in the review of 4 high-quality (level I) trials, 5 case series and 18 case reports: • 2 dystonic reactions (Richards, 1997; Shen, 2008) • 2 cases of rigidity without hyperthermia concerning for mild NMS (Henderson, 2011) • circulatory collapse (Koerselman and Goslinga, 1987)	ATS -associated agitation and psychosis
Any side effects	N/A	Systematic review: Lee 2018[24] (Moderate)	Aripiprazole "may have unsafe side effects" (Coffin 2012 (10 mg/day 12 weeks); Tiihonen 2007 (15 mg/day 20 weeks)) Risperidone "well tolerated." (Meredith 2007 (3.6 mg/day 4 weeks); Meredith 2009 (25 mg OD 8 weeks); Solhi 2014 (2 mg OD 3 weeks))	ATS, not intoxicated patients
		Meta-analysis: Indave 2016 [17] (Not assessed)	**No significant difference** between antipsychotics and placebo in number of participants with CoUD experiencing at least one side effect: 6 RCTs, 291 participants, RR 1.01, 95% CI (0.93, 1.10). • Brown 2010 (400 to 800 mg/day 12 weeks); Brown 2012 (400 mg/day 10 weeks); Hamilton 2009 (20 mg/day 16 weeks); Meini 2010 (Aripriprazol 10 mg/day or ropinirole 1.5 mg x 3/day 12 weeks); Reid 2005 (10 mg/day 15 days); Tapp 2015 (400 mg/day 12 weeks). **No significant difference** in sub-analyses for lamotrigine, olanzapine or quetiapine vs placebo.	CoUD, not intoxicated patients
Extrapyra-midal symptoms	N/A	Meta-analysis: Shoptaw 2009[25] (Not assessed)	**Olanzapine > Haloperidol** in improved extrapyramidal symptoms in 1 RCT • Leelahanaj 2005 (n=58 ATS-induced psychosis, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d)	ATS- associated agitation and psychosis
Extrapyra-midal adverse effects	N/A	Systematic review: Richards 2015[18] (Moderate)	**15 adverse extrapyramidal events occurred in 287 patients (5.2%)** receiving antipsychotics for ATS toxicity in the review of 4 high-quality (level I) trials, 5 case series and 18 case reports.	ATS -associated agitation and psychosis
Global state	N/A	Meta-analysis: Shoptaw 2009[25] (Not assessed)	**No difference** between olanzapine and haloperidol in improvements on the Clinical Global Impression (CGI) scale from baseline to endpoint in 1 RCT. Both groups improved at endpoint (paired t test, $p<0.001$). • Leelahanaj 2005 (n=58 ATS psychosis, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d)	ATS- associated agitation and psychosis

Benzodiazepines and other GABA-active agents

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments

Critically Important Outcomes				
Psychotic symptoms	Low	Systematic review: Richards 2015[18] (Moderate)	**Droperidol > Lorazepam** in reducing psychosis in 1 high quality prospective randomized trial: • Richards et al., 1997; n=146 Methamphetamine intoxication; Summary: Droperidol superior to lorazepam for prolonged sedation (P < 0.05). AEs=1, single dystonic reaction **Lorazepam + Haloperidol + Risperidone** effective in reducing psychosis in 1 case series: • Kasick et al., 2012; n=2 Mephedrone intoxication; Summary: Resolution of psychosis after lorazepam, haloperidol and risperidone. AEs=0 **Droperidol + Lorazepam** effective in reducing psychosis in 1 case report: • Thornton et al., 2012 n=1; Stimulant: MDPV Flephedrone intoxication; Summary: Resolution of psychosis with droperidol and lorazepam. AEs=0	ATS - associated agitation and psychosis
Adverse events	Low	Systematic review: Richards 2016[23] (Low)	**1 adverse event out of 234 patients (0.4%)** treated with benzodiazepines for acute cocaine toxicity**:** "one adverse event in a case report in which cardiopulmonary arrest occurred during lorazepam administration"	Acute cocaine toxicity
		Systematic review: Richards 2015[18] (Moderate)	**3 adverse events out of 139 patients (2.2%)** treated for ATS-associated agitation and psychosis reported in 1 high quality prospective randomized study (n=74), 6 case series (n=53) and 12 case reports. "All were associated with failure to achieve adequate sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (p. 3). • Caldicott et al., 2003 Case report p-methoxyamphetamine-related (PMA) required intubation for chemical restraint, failed sedation with midazolam • Kiely et al., 2009 Case report MA-related death from fatal ingestion, multiple doses lorazepam failed to achieve sedation • Lusthof et al., 2011 Case report Mephedrone-related extreme agitation and death, midazolam not causative Over-sedation with respiratory depression and paradoxical agitation did not occur.	ATS - associated agitation and psychosis
Important Outcomes				
Treatment failure	N/A	Systematic review: Richards 2016[23] (Low)	**8 treatment failures out of 234 patients (3.4%)** treated with benzodiazepines for acute cocaine toxicity	Acute cocaine toxicity
		Systematic review: Richards 2015[18] (Moderate)	**3 cases of under-sedation out of 139 patients (2.2%)** • See adverse events for details	ATS - associated agitation and psychosis

Psychosis: Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Glasner-Edwards & Mooney 2014[2]	• "Ideally, treatment of individuals with co-occurring psychosis and MA use should address both the psychotic symptoms or disorder (ie, including ongoing psychiatric evaluation and treatment as indicated) and the MA use disorder, to facilitate sufficient periods of abstinence to facilitate the clinician make an informed differential diagnosis." (Glasner-Edwards & Mooney 2014, p9) [2] • Long-term treatment for MA-induced psychosis – Psychosocial treatment (CBT, CM, 12 step). "Evidence-based behavioral interventions targeting stimulant addiction, such as the Matrix Model (which combines cognitive behavioral therapy [CBT] with family education and self-help participation), effectively engage psychotic MA users in treatment, and reductions in MA use among individuals with psychotic disorders are comparable to those observed among MA dependent adults without psychosis [10]." (Glasner-Edwards & Mooney 2014, p4) [2] • "If clinically indicated, psychiatric medications may be prescribed to manage comorbid conditions such as major depression, anxiety disorders, or persistent psychotic disorders. Given that negative affect states, such as depression or anxiety have been demonstrated to increase relapse risk and worsen treatment outcomes among MA users (see Glasner-Edwards, [11,96]), amelioration of persistent symptoms with psychosocial treatment or pharmacotherapy is important in individuals with co-occurring addiction and mental health disorders." (Glasner-Edwards & Mooney 2014, p11)[2] • "though no medications have been FDA approved for the treatment of MA use disorder, several medications have shown preliminary benefit in reducing MA use in some studies, including bupropion[93] naltrexone [97], mirtazapine [98], and methylphenidate [99]." (Glasner-Edwards & Mooney 2014, p11)[2]	
Chiang 2019[5]	Cognitive behavioral therapy • "Although no studies have been conducted on the efficacy of CBT for MAP patients, CBT represents a promising treatment method for medication resistant patients. CBT treatment methods such as the Matrix Model should be adjusted and applied for use in MAP populations (Glasner-Edwards & Mooney, 2014, p7)." (p. 7) Mindfulness-based relapse prevention • Effective for methamphetamine use disorder • Effective for psychotic disorder "A meta-analysis of mindfulness-based interventions for psychosis revealed that the intervention resulted in significantly reduced positive and negative psychotic symptoms when compared with TAU controls (Louise, Fitzpatrick, Strauss, Rossell, & Thomas, 2018)." (p. 8) Exercise-based therapies • Effective for methamphetamine use disorder • Effective for psychotic disorder "Exercise-based therapies have been shown to result in improvements to both positive and negative symptoms in schizophrenia and help ameliorate the damaging metabolic side effects associated with antipsychotic medications (Archer & Kostrzewa, 2015; Morris et al., 2018)." (p. 9)	Narrative review

Schizophrenia or schizoaffective disorder

Schizophrenia: Systematic Reviews and Meta-Analyses

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
SUD symptom severity	Low	Systematic review: Sabioni 2013[26] (Not assessed)	Conventional antipsychotics • "Typical antipsychotics and the monoamine transporter antagonist did not improve the symptoms of cocaine dependence in schizophrenic patients and sometimes even exacerbated them" (p. 487). • Sayers (2005), Smelson (2006b), Perry (2005) Atypical antipsychotics • "atypical antipsychotics, especially aripiprazole, effectively reduced cocaine use. In some cases, however, the same medication presented opposite results in relation to cocaine abuse or dependence." (p 487) • Akerele (2007), Beresford (2005), McRae-Clark (2009), Sayers (2005), Smelson (2002), Smelson (2006b)	Cocaine use disorder
Treatment retention	Low	Meta-analysis: Krause 2019[27] (High)	Dropout due to treatment non-response • **No difference** Haloperidol vs Olanzapine in 1 study: Tsuang (2002) • **No difference** Olanzapine vs Risperidone in 1 study: Akerele (2007)	Cocaine use disorder
Stimulant use	Low	Meta-analysis: Krause 2019[27] (High)	**No difference** between Aripiprazole vs Perphenazine in stimulant use (n) • Beresford (2017) **No difference** between Haloperidol vs Olanzapine in stimulant use (n) • Sayers (2005), Smelson (2006b)	Cocaine use disorder
		Systematic review: Sabioni 2013[26] (Not assessed)	**Atypical > conventional antipsychotics:** "atypical antipsychotics, especially aripiprazole, effectively reduced cocaine use" (p 487) compared to conventional antipsychotics (4 studies) • Akerele (2007), Sayers (2005), Smelson (2002), Smelson (2006b) **Aripiprazole** decreased stimulant use in two open-label single-arm trials • Beresford (2005), McRae-Clark (2009) Mixed results for Risperidone vs Conventional antipsychotic in relapse • Akerele (2007), Smelson (2002)	Cocaine use disorder

Schizophrenia: Individual Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Beresford 2017[28]	RCT	(1) Aripiprazole (2) Perphenazine	Schizophrenia and comorbid cocaine dependence	**Cocaine use** (UDS): n.s.d. in negative urine samples **Cocaine craving**: Significantly decreased in aripiprazole at 6 weeks	In Murthy 2019[29]

Brown 2005[30]	Pre-post open-label 12 wks	(1) Aripiprazole: up to 30 mg/day Also contingency management	N = 19 participants with bipolar disorder I or II or schizoaffective disorder and concurrent substance dependence	**Cocaine use**: No difference in days of use (d= −0.78) **Alcohol Use**: No difference in days of use (d= −0.36) **Cocaine craving** (VAS): Significant decrease (d= 0.91) **Alcohol craving** (VAS): Significant decrease (d= 1.02) **Depressive symptoms** (HAM-D): Significant decrease (d= 1.40) **Manic symptoms** (YMRS): Significant decrease (d= 0.74)	In Coles 2019[31]

HAMD, hamilton depression scale
YMRS, young mania rating scale
VAS, visual analogue scale

Bipolar Disorder

Bipoloar Disorder: Systematic Reviews and Meta-Analyses

Outcomes	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
SUD symptom severity	Low	Systematic review: Sepede 2018[32] (Not assessed)	Atypical antipsychotics • "AAPs [atypical antipsychotics] are effective on mood symptoms, but not equally efficacious on SUD. We also observed a better efficacy for OLTs, with respect to DB-RCTs." (p. 189) • "9 of 10 studies [also] allowed treatment with benzodiazepines (BDZs), mood stabilizers (MSs) or antidepressants (ADs)" (p. 189)	Mixed SUD. Not stimulant specific.
Important Outcomes				
Substance use	N/A	Meta-analysis: Stokes 2020[33] (Not assessed)	<u>Pharmacotherapy vs placebo</u> **No difference** in likelihood of abstinence at the end of treatment (4 studies, OR (95% CI) = 0.97 (0.59, 1.58), p=0.9) • Brown 2007 (n=44 CoUD & Bipolar, Citicoline add-on up to 2000 mg/d vs placebo); Brown 2010 (Quetiapine 400-800 mg/d); Brown 2012a (n=48 ATStUD & Bipolar/MDD, Lamotrigine add-on 400 mg/d vs placebo); Brown 2015 (n=130 CoUD & Bipolar, Citicoline add-on up to 2,000 mg/d vs placebo)	Cocaine use disorder
		Meta-analysis: Coles 2019[31] (Not assessed)	**Bupropion add-on** to current mood stabilizer had a large effect on substance use in 1 RCT (n=12, M(sd)= 2.23 (1.4), 95% CI (0.99, 3.47) • Sepede 2014 (n=12 CoUD & Bipolar, Bupropion add-on 150 mg/d vs no add-on to existing bipolar I treatment) **Quetiapine** had a small effect on substance use in 8 studies (M(sd)= 0.20 (0.5), CI: −0.8 to +1.2). Only 2 stimulant use disorder studies:	Sub-analyses for StUD

			• Nejtek 2008 (n=80 CoUD/MaUD & Bipolar, quetiapine mean 303 mg/d vs risperidone mean 3.1 mg/d); Brown 2002 (n=14 CoUD & Bipolar, quetiapine add-on median 275 mg/d) **Lamotrigine** had a moderate effect on substance use in 4 studies (M(sd)= 0.76 0.99), CI: −1.22 to 2.74) • Brown 2003 (n=30 CoUD & Bipolar, lamotrigine up to 300 mg/d); Brown 2006 (n=52 CoUD & Bipolar, lamotrigine up to 300 mg/d); Brown 2012a (n=48 ATStUD & Bipolar/MDD, Lamotrigine add-on 400 mg/d); Rubio 2006 (AUD, lamotrigine up to 300 mg/d) **Citicoline add-on** to current mood stabilizer had a small effect on substance use in 3 studies (M(sd)= 0.12 (0.32), CI −0.52 to 0.76; OR 1.26, 95% CI 0.395 to 4.043, p = 0.69; OR 6.41, 95% CI 1.25 to 33.33 • Brown 2007 (n=44 CoUD & Bipolar, up to 2000 mg/d vs placebo); Brown 2012b (n=48 MaUD & Bipolar/MDD, up to 2000 mg/d vs placebo; Brown 2015 (n=130 CoUD & Bipolar, up to 2,000 mg/d vs placebo)	
Mood outcomes	N/A	Meta-analysis: Coles 2019[31] (Not assessed)	**Bupropion add-on** to current mood stabilizer had a large effect on mood outcomes in 1 RCT (M(sd)= 1.50 (2.08), 95% CI −2.66 to 5.66) • Sepede 2014 (n=12 CoUD & Bipolar, Bupropion add-on 150 mg/d vs no add-on to existing bipolar I treatment) **Quetiapine** had a small effect on substance use in 8 studies (M(sd)= 0.41 (0.78), CI: −1.15 to 1.97) (2 stimulant use disorder studies) • Nejtek 2008 (n=80 CoUD/MaUD & Bipolar, quetiapine mean 303 mg/d vs risperidone mean 3.1 mg/d); Brown 2002 (n=14 CoUD & Bipolar, quetiapine add-on median 275 mg/d) **Lamotrigine** had a moderate effect on mood outcomes in 4 studies (M(sd)= 0.70 (0.66), CI: −0.62 to 2.02) (3 stimulant use disorder studies) • Brown 2003 (n=30 CoUD & Bipolar, lamotrigine up to 300 mg/d); Brown 2006 (n=52 CoUD & Bipolar, lamotrigine up to 300 mg/d); Brown 2012a (n=48 ATStUD & Bipolar/MDD, Lamotrigine add-on 400 mg/d); Rubio 2006 (AUD, lamotrigine up to 300 mg/d) **No effect of citicoline add-on** to current on mood outcomes in 3 studies (M(sd)= −0.07 (0.39), CI: −0.85 to 0.71) • Brown 2007 (n=44 CoUD & Bipolar, up to 2000 mg/d vs placebo); Brown 2012b (n=48 MaUD & Bipolar/MDD, up to 2000 mg/d vs placebo); Brown 2015 (n=130 CoUD & Bipolar, up to 2,000 mg/d vs placebo)	Mixed SUD
Treatment acceptability	N/A	Meta-analysis: Stokes 2020[33] (Not assessed)	**Pharmacotherapy > Placebo** in treatment-associated dropout compared among patients with cocaine, MA, and alcohol use disorder (11 studies, RR (95% CI) = 0.8 (0.66, 0.98), p=0.003)	Mixed SUD

			• Brown (2010); Brown (2014); Stedman (2010); Brown (2012a); Salloum (2005); Sylvia (2016); Brown (2007); Brown (2012b); Brown (2015); Brown (2009); Tolliver (2012) **Citicoline add-on > Placebo** (CoUD/MaUD) (3 studies, RR (95% CI) = 0.63 (0.48, 0.84), p=0.002 • Brown 2007 (n=44 CoUD & Bipolar, up to 2000 mg/d vs placebo); Brown 2012b (n=48 MaUD & Bipolar/MDD, up to 2000 mg/d vs placebo); Brown 2015 (n=130 CoUD & Bipolar, up to 2,000 mg/d vs placebo) **No difference** between Quetiapine and Placebo in treatment-associated dropout among patients with cocaine and alcohol use disorder. (3 studies) • Brown (2010), Brown (2014), Stedman (2010) **No difference** between Anticonvulsants and Placebo (Cocaine and Alcohol) (3 studies) • Brown (2012a), Salloum (2005), Sylvia (2016)	

Bipolar Disorder: Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Comments
Brown 2002[34]	Open-label 12 wks	Quetiapine add-on: Median dose 275 mg/d Also contingency management	N = 17 outpatients with bipolar I or II disorder and cocaine dependence	14 completed Cocaine use: No significant changes (d= −0.33). Cocaine craving (CCQ): Significant decrease (d= 0.43) Manic symptoms (YMRS): Significant decrease (d= 1.26) Depressive symptoms (HDRS): Significant decrease (d= 1.26)	In Coles 2019[31]
Brown 2003[35]	Open-label 12 wks Outpatient	Lamotrigine: Up to 300 mg/day Also contingency management	N = 30 outpatients with bipolar I, II or NOS disorder and cocaine dependence	Cocaine use: No reduction (d= −0.33) Cocaine craving (CCQ): Significant decrease (d=0.95) Depressive symptoms (HAM-D): Significant decrease (d=0.55) Manic symptoms (YMRS): Significant decrease (d=0.83)	In Coles 2019[31]
Brown 2006[36]	Open-label 36 wks Outpatient	Lamotrigine: Up to 300 mg/day Additional treatment not reported	N = 62 outpatients with bipolar I, II, or NOS disorder and cocaine dependence	Cocaine use: No reduction (d= -0.15) Cocaine craving (CCQ):): Significant decrease (d= 0.73) Depressive symptoms (HDRS):): Significant decrease (d=0.8) Manic symptoms (YMRS):): Significant decrease (d=0.64)	In Coles 2019[31]

Brown 2005[30]	Pre-post 12 wks	Aripiprazole: up to 30 mg/day Also contingency management	N = 19 participants with bipolar disorder I or II or schizoaffective disorder and concurrent substance dependence. open-label	Days of Cocaine Use: No difference (d= −0.78) Days of Alcohol Use: No difference (d= −0.36) Cocaine craving (VAS): Significant decrease (d= 0.91) Alcohol craving (VAS): Significant decrease (d= 1.02) Depressive symptoms (HAM-D): Significant decrease (d= 1.40) Manic symptoms (YMRS): Significant decrease (d= 0.74)	In Coles 2019[31]
Brown 2007[37]	RCT 12 wks Outpatients	(1) Citicoline add-on up to 2000 mg/d (2) Placebo Additional treatment not reported	N=44 patients with bipolar disorder (history of mania or hypomania) and cocaine dependence (all participants had at least one additional SUD)	Cocaine use (UDT+): Citicoline was associated with significantly fewer cocaine positive urine screens compared to placebo (OR = 6.41; 95% CI, 1.25-33.33.) Depressive symptoms (IDS-SR): No diff between groups (d =−0.65) Manic symptoms (YMRS): No diff between groups (d =−0.04)	In Coles 2019[31]
Brown 2012b[38]	RCT, double-blind 12 wks Outpatient	(1) Citicoline add-on up to 2000 mg/d (n=28) (2) Placebo (n=20) Additional treatment not reported	N = 48 patients meeting criteria for bipolar I, II or NOS disorders, currently depressed or major depressive disorder and amphetamine dependence	MA use: No sig difference between groups @ tx end (OR = 1.26, 95% CI 0.395-4.043, p = 0.69). Depressive symptoms (ICD-S): Citicoline > Placebo @ tx end (d=0.56)	In Coles 2019[31]
Brown 2012a[39]	RCT, double-blond 10 wks	(1) Lamotrigine add-on up to 400 mg/d (2) Placebo	N = 120 outpatients with bipolar I, II, or NOS disorders currently depressed or mixed mood, and cocaine dependence	CCQ: No sig diff between groups @ tx end (d = −0.12) Dollars spent on cocaine: Lamotrigine group showed a greater decrease in the amount spent on cocaine @ tx end (d = 0. 377) HDRS: No sig diff between groups @ tx end (d = −0.104) YMRS: No sig diff between groups @ tx end (d = −0.135)	In Coles 2019[31]
Brown 2015[40]	RCT, double-blind 12 wks Outpatient	(1) Citicoline add-on mean 2000 mg/d (n=61) (2) Placebo (n=61) Plus 16 sessions of cognitive behavioral	N=130 patients with bipolar I disorder (depressed or mixed mood state) and cocaine dependence on current treatment with a mood stabilizer	Cocaine use (UDT+): Significant decline compared with placebo at the end of treatment (d = 0.44) Cocaine craving (CCQ): No diff between groups (d = −0.208). Depressive symptoms (HDRS): No diff between groups (d= −0.16)	In Murthy 2019[29] and Coles 2019[31]

		therapy (for BPD & SUD)		Manic symptoms (YMRS): No diff between groups (d= −0.058).	
Nejtek 2008[41]	RCT 20 wks Outpatient	(1) Quetiapine: Mean dose 303.6 ± 151.9 mg/d (n=42) (2) Risperidone: Mean 3.1 ± 1.2 mg/d (n=38)	N=80 adults age 20-50 with concurrent DSM-IV-defined bipolar I or II disorder and cocaine or MA dependence. Excluded if met DSM-IV criteria for substance-induced mood disorder, had any other substance dependence	Use: Significant decrease in both groups Craving: Significant decrease in both groups (Quetiapine d=1.07, Risperidone d=0.93) Depressive symptoms (ICD-C-30): Significant decrease in both groups (Quetiapine d=1.22, Risperidone d=1.11) Manic symptoms (YMRS): Significant decrease in both groups (Quetiapine d=1.15, Risperidone d=1.34) Both medications were well tolerated.	In Coles 2019[31]
Sepede 2014[42]	open-label 4 wks	(1) Bupropion add-on 150 mg/d (n=5) (2) No add-on to existing bipolar I treatment (n=7) Additional treatment not reported	N=12 currently depressed participants with bipolar disorder type I and comorbid cocaine dependence.	No dropouts **Cocaine use** (DAST): Bupropion > No rx @ tx end (d = 2.23). Depressive symptoms (HAMD): Bupropion > No rx @ tx end (d= 3.57). Manic symptoms (YMRS): No difference between groups @ tx end (d= −0.58)	In Coles 2019[31]

CCQ, cocaine consumption questionnaire
DAST, drug abuse screening test;
HAMD, hamilton depression scale
HDRS, hamilton depression rating scale
VAS, visual analogue scale
YMRS, young mania rating scale

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019:59.

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Holmwood C, Gowing L. *Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults*. Drug and Alcohol Services South Australia (DASSA); 2019.

NSW Ministry of Health. *Drug and Alcohol Withdrawal Clinical Practice Guidelines (Reviewed 2018)*. NSW Health; 2008. Accessed September 16, 2021. www.health.nsw.gov.au

Beaulieu S, Saury S, Sareen J, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. *Ann Clin Psychiatry*. 2012;24(1):38-55.

Other Resources

Source	Resources	Comments
SAMHSA	TIP 42 (https://store.samhsa. gov/product/tip-42-substance-usetreatment-persons-co-occurring-disorders/ PEP20-02-01-004).	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Almost all systematic and meta-analysis evidence for treating symptoms of psychosis is from stimulant-induced or unspecified causes of psychosis.	Large beneficial effect for stimulant-induced psychosis. Large for pre-existing psychosis. Large beneficial effect for stimulant-induced mania. Large for pre-existing mania.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Acute and chronic effects of antipsychotic medications. Differences between typical and atypical antipsychotics.	Moderate undesirable effect for stimulant-induced psychosis. Moderate for pre-existing psychosis. Moderate undesirable effect for stimulant-induced mania. Moderate for pre-existing mania.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Substantial for stimulant-induced psychosis, pre-existing psychosis, stimulant-induced mania, pre-existing mania.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Side effects of medication may reduce acceptability	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Medications are relatively easy to access	☐ No ☐ Probably no ☐ Uncertain

		☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Treatment does not differ between stimulant-induced and pre-existing symptoms of psychosis or mania.

Subgroup Considerations

None noted

Implementation Considerations

- In patients with a history of psychosis (substance-induced or pre-existing), do not treat StUD with topiramate, modafinil, or psychostimulant medications.

References

1. Sulaiman AH, Gill JS, Said MA, Zainal NZ, Hussein HM, Guan NC. A randomized, placebo-controlled trial of aripiprazole for the treatment of methamphetamine dependence and associated psychosis. *Int J Psychiatry Clin Pract*. 2013;17(2):131-138. doi:10.3109/13651501.2012.667116
2. Glasner-Edwards S, Mooney L. Methamphetamine psychosis: epidemiology and management. *CNS Drugs*. 2014;28(12):1115-1126. doi:10.1007/s40263-014-0209-8
3. McKetin R, Dawe S, Burns RA, et al. The profile of psychiatric symptoms exacerbated by methamphetamine use. *Drug Alcohol Depend*. 2016;161:104-109. doi:10/gc8rz4
4. Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de
5. Chiang M, Lombardi D, Du J, et al. Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options. *Hum Psychopharmacol*. 2019;34(5):e2710. doi:10.1002/hup.2710
6. Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004
7. McKetin R, Leung J, Stockings E, et al. Mental health outcomes associated with the use of amphetamines: A systematic review and meta-analysis. *EClinicalMedicine*. 2019;16:81-97. doi:10.1016/j.eclinm.2019.09.014
8. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
9. Salo R, Flower K, Kielstein A, Leamon MH, Nordahl TE, Galloway GP. Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Res*. 2011;186(2-3):356-361. doi:10.1016/j.psychres.2010.09.014
10. McKetin R, Baker AL, Dawe S, Voce A, Lubman DI. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res*. 2017;251:349-354. doi:10.1016/j.psychres.2017.02.028

11. McKetin R, Najman JM, Baker AL, et al. Evaluating the impact of community-based treatment options on methamphetamine use: findings from the Methamphetamine Treatment Evaluation Study (MATES): Methamphetamine use treatment outcomes. *Addiction*. 2012;107(11):1998-2008. doi:10.1111/j.1360-0443.2012.03933.x
12. Shelly J, Uhlmann A, Sinclair H, et al. First-Rank Symptoms in Methamphetamine Psychosis and Schizophrenia. *Psychopathology*. 2016;49(6):429-435. doi:10/gn76z3
13. Vergara-Moragues E, Mestre-Pintó JI, Gómez PA, Rodríguez-Fonseca F, Torrens M, González-Saiz F. Can symptoms help in differential diagnosis between substance-induced vs independent psychosis in adults with a lifetime diagnosis of cocaine use disorder? *Psychiatry Res*. 2016;242:94-100. doi:10/f835jw
14. Wang LJ, Lin SK, Chen YC, et al. Differences in Clinical Features of Methamphetamine Users with Persistent Psychosis and Patients with Schizophrenia. *Psychopathology*. 2016;49(2):108-115. doi:10/gn76x4
15. Srisurapanont M, Likhitsathian S, Suttajit S, et al. Efficacy and dropout rates of antipsychotic medications for methamphetamine psychosis: A systematic review and network meta-analysis. *Drug Alcohol Depend*. 2021;219:108467. doi:10.1016/j.drugalcdep.2020.108467
16. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
17. Indave BI, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online March 19, 2016. doi:10.1002/14651858.CD006306.pub3
18. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10.1016/j.drugalcdep.2015.01.040
19. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-analysis. *J Gen Intern Med*. 2019a;34(12):2858-2873. doi:10.1007/s11606-019-05074-8
20. Chan B, Freeman M, Ayers C, et al. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. *Drug Alcohol Depend*. 2020;216:108193. doi:10.1016/j.drugalcdep.2020.108193
21. Chan B, Freeman M, Kondo K, et al. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. *Addiction*. 2019b;114(12):2122-2136. doi:10.1111/add.14755
22. Kishi T, Matsuda Y, Iwata N, Correll CU. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2013;74(12):e1169-1180. doi:10.4088/JCP.13r08525
23. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090
24. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018;191:309-337. doi:10.1016/j.drugalcdep.2018.06.038
25. Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online January 21, 2009. doi:10.1002/14651858.CD003026.pub3
26. Sabioni P, Ramos A, Galduroz J. The Effectiveness of Treatments for Cocaine Dependence in Schizophrenic Patients: A Systematic Review. *Curr Neuropharmacol*. 2013;11(5):484-490. doi:10/gn757j
27. Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutsmiedl K, Leucht S. Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2019;29(1):32-45. doi:10/ggxbt6
28. Beresford T, Buchanan J, Thumm EB, Emrick C, Weitzenkamp D, Ronan PJ. Late Reduction of Cocaine Cravings in a Randomized, Double-Blind Trial of Aripiprazole vs Perphenazine in Schizophrenia and Comorbid Cocaine Dependence. *J Clin Psychopharmacol*. 2017;37(6):657-663. doi:10.1097/JCP.0000000000000789

29. Murthy P, Mahadevan J, Chand PK. Treatment of substance use disorders with co-occurring severe mental health disorders. *Curr Opin Psychiatry*. 2019;32(4):293-299. doi:10.1097/YCO.0000000000000510
30. Brown ES, Jeffress J, Liggin JD, Garza M, Beard L. Switching out- patients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin psychiatry*. 2005;66(6):756-760.
31. Coles AS, Sasiadek J, George TP. Pharmacotherapies for co-occurring substance use and bipolar disorders: A systematic review. *Bipolar Disord*. 2019;21(7):595-610. doi:10/gn757b
32. Sepede G, Lorusso M, Spano MC, Di Nanno P, Di Iorio G, Di Giannantonio M. Efficacy and Safety of Atypical Antipsychotics in Bipolar Disorder With Comorbid Substance Dependence: A Systematic Review. *Clin Neuropharmacol*. 2018;41(5):181-191. doi:10/gfdgrh
33. Stokes PRA, Jokinen T, Amawi S, et al. Pharmacological Treatment of Mood Disorders and Comorbid Addictions: A Systematic Review and Meta-Analysis. *Can J Psychiatry Rev Can Psychiatr*. 2020;65(11):749-769. doi:10.1177/0706743720915420
34. Brown ES, Nejtek VA, Perantie DC, Bobadilla L. Quetiapine in bipolar disorder and cocaine dependence. *Bipolar Disord*. 2002;4(6):406-411. https://doi.org/10.1034/j.1399-5618.2002.02229.x
35. Brown ES, Nejtek VA, Perantie DC, Orsulak PJ, Bobadilla L. Lamotrigine in patients with bipolar disorder and cocaine dependence. *J Clin psychiatry*. 2003;64(2):197-201.
36. Brown ES, Perantie DC, Dhanani N, Beard L, Orsulak P, Rush AJ. Lamotrigine for bipolar disorder and comorbid cocaine dependence: a replication and extension study. *J Affect Disord*. 2006;93(1–3):219-222. https://doi.org/10.1016/j.jad.2006.02.001
37. Brown ES, Gorman AR, Hynan LS. A randomized, placebo- controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. *J Clin Psychopharmacol*. 2007;27(5):498-502. doi: 10.1097/JCP.0b013e31814db4c4
38. Brown ES, Gabrielson B. A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. *J Affect Disord*. 2012b;143(1–3):257-260. https://doi.org/10.1016/j.jad.2012.05.006
39. Brown ES, Sunderajan P, Hu LT, Sowell SM, Carmody TJ. A randomized, double-blind, placebo-controlled, trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. *Neuropsychopharmacology*. 2012a;37(11):2347-2354. https://doi.org/10.1038/npp.2012.90
40. Brown ES, Todd JP, Hu LT, et al. A randomized, double-blind, placebo-controlled trial of citicoline for cocaine dependence in bipolar I disorder. *Am J Psychiatry*. 2015;172(10):1014-1021. https://doi.org/10.1176/appi.ajp.2015.14070857
41. Nejtek VA, Avila M, Chen LA, et al. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *J Clin Psychiatry*. 2008;69(8):1257-1266. doi:10.4088/jcp.v69n0808
42. Sepede G, Di lorio G, Lupi M, et al. Bupropion as an add-on therapy in depressed bipolar disorder type I patients with comorbid cocaine dependence. *Clin Neuropharmacol*. 2014;37(1):17-21. Doi: 10.1097/WNF.0000000000000011

Table 19. Psychosis Taper

Recommendation: If stimulant-induced psychosis or mania is suspected, clinicians should consider a gradual taper off antipsychotic medication after a period of remission of psychotic symptoms.

Clinical Question Summary

Clinical Question	1. What is the optimal duration of antipsychotic treatment for persons who are presumed to be experiencing stimulant-induced psychosis or mania? 2. What is the clinical effectiveness of different antipsychotic tapering strategies?
Population	Patients with suspected stimulant stimulant-induced psychosis or mania
Intervention	Gradual dose taper to complete discontinuation of antipsychotic medication
Comparison	Continuation of antipsychotic medication
Main Outcomes	Rebound symptoms, Treatment retention, Stimulant use, Adverse events
Setting	Hospital, ER, Inpatient or outpatient specialty SUD treatment
Background & Definitions	Treating stimulant psychosis vs treating StUD in underlying psychosis Methamphetamine associated psychosis is associated with a spectrum of clinical presentations, including delusional experiences to persistent psychosis and cognitive impairment (Arunogiri 2020)[1]
Abbreviations	**ARDA:** Amphetamine, related derivatives, and analogues, **ATS:** Amphetamine-type stimulant, **AUD**: Alcohol use disorder, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **OUD**: Opioid Use Disorder, **RCT**: Randomized Control Trial, **SMI**: Severe mental illness, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No relevant research was identified regarding the optimal duration of antipsychotic treatment or the clinical effectiveness of antipsychotic tapering strategies for the treatment of persons who are presumed to be experiencing stimulant-induced psychosis or mania.

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Holmwood C, Gowing L. *Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults*. Drug and Alcohol Services South Australia (DASSA); 2019. https://www.sahealth.sa.gov.au/wps/wcm/connect/Public%20Content/SA%20Health%20Internet/Resources/Policies/Acute%20Presentations%20Related%20to%20Methamphetamine%20Use%20Clinical%20Guideline

NSW Ministry of Health. *Drug and Alcohol Withdrawal Clinical Practice Guidelines (Reviewed 2018)*. NSW Health; 2008. Accessed September 16, 2021. www.health.nsw.gov.au

Psychosis: Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Glasner-Edwards & Mooney 2014[2]	• "If clinically indicated, psychiatric medications may be prescribed to manage comorbid conditions such as major depression, anxiety disorders, or persistent psychotic disorders. Given that negative affect states, such as depression or anxiety have been demonstrated to increase relapse risk and worsen treatment outcomes among MA users (see Glasner-Edwards, [11,96]), amelioration of persistent symptoms with psychosocial treatment or pharmacotherapy is important in individuals with co-occurring addiction and mental health disorders." (Glasner-Edwards & Mooney 2014, p11)[2]	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No research evidence was found regarding antipsychotic medication discontinuation. Avoid unnecessary exposure to the acute and chronic effects of antipsychotic medications, which differs by agent. Desirable effects from protecting against unnecessary exposure and development of known adverse effects of chronic antipsychotic or mood stabilizing (eg, lithium, valproate) medications. known risk of continuation of antipsychotics or mood stabilizers (eg, lithium, valproate).	**For treatment of stimulant-induced psychosis,** Moderate for individuals with pre-existing psychosis. Large for individuals without a history of previous episodes of stimulant psychosis, no current stimulant use, with remission of psychosis symptoms. … for individuals with a history of previous episodes of stimulant psychosis **For treatment of stimulant-induced mania**, Moderate for individuals with pre-existing mania. Large for individuals without a history of previous episodes of stimulant mania, no current stimulant use, with remission of manic symptoms … for individuals with a history of previous episodes of stimulant psychosis	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No research evidence was found regarding undesirable effects	Currently no reliable evidence that helps us predict the level of risk of recurrent psychosis from tapering off antipsychotics (psychosis history, symptom severity).	☐ None ☐ Small ☐ Moderate

In some cases psychotic symptoms may return, undesirable effect from potential risk of recurrence of psychosis.	**For treatment of stimulant-induced psychosis,** Moderate for pre-existing psychosis. Moderate for stimulant-induced psychosis. Small for individuals w/o history of previous episodes of stimulant psychosis, no current stimulant use, with remission of psychosis symptoms. **For treatment of stimulant-induced mania**, Moderate for pre-existing mania.	☐ Large ☒ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	If psychosis is severe, desirable would outweight undesirable The worse the psychosis symptoms, the more indicated pharmacotherapy would be This recommendation is in line with general psychiatry	☐ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☒ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	Mostly observational	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☒ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

If psychosis is severe, desirable would outweight undesirable. The worse the psychosis symptoms, the more indicated pharmacotherapy would be. This recommendation is in line with general psychiatry

Subgroup Considerations

None noted

Implementation Considerations

No implementation concerns

References

1. Arunogiri S, McKetin R, Verdejo-Garcia A, Lubman DI. The Methamphetamine-Associated Psychosis Spectrum: a Clinically Focused Review. *Int J Ment Health Addiction*. 2020;18(1):54-65. doi:10.1007/s11469-018-9934-4
2. Glasner-Edwards S, Mooney LJ. Methamphetamine Psychosis: Epidemiology and Management. *CNS Drugs*. 2014;*28*(12):1115-1126. https://doi.org/10.1007/s40263-014-0209-8

Table 20. Other Symptoms

Recommendation: When developing a treatment plan for symptoms of depression, anxiety, insomnia, and/or attentional problems observed during periods of stimulant use or withdrawal, clinicians should:

a. Consider pharmacotherapy based on symptom severity and duration, even if symptoms are stimulant induced.
b. Consider whether the patient's clinical presentation follows the expected time-course of stimulant-induced symptoms given the phase of use (ie, active use, waning intoxication, acute withdrawal, post-acute withdrawal, post-withdrawal abstinence) or are present at other times.

Clinical Question Summary

Clinical Question	1. Should clinicians use pharmacotherapy to treat depression, anxiety, insomnia, and/or attentional problems in patients with stimulant use disorder if it is unclear whether the condition is pre-existing or stimulant-induced? 2. What contextual factors and implementation strategies may influence the decision to use pharmacotherapy? 3. What are the most effective and appropriate pharmacotherapies for treating depression, anxiety, insomnia, and/or attentional problems in patients with stimulant use disorder?
Population	Patients with stimulant use disorder experiencing depression, anxiety, insomnia, and/or attentional problems
Intervention	Pharmacotherapy
Comparison	No pharmacotherapy
Main Outcomes	StUD symptoms, Co-occurring disorder symptoms, Treatment retention, Adverse events
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Notes • Some studies, even ones investigating the effectiveness of medications for StUD allow symptomatic medications on an as-needed basis. For example, in McGregor's (2008) study of mirtazapine vs modafinil, diazepam (5–10 mg) for anxiety and either nitrazepam (5–10 mg) or temazepam (10–20 mg) for insomnia were available. • "For MA use, people appear more likely to have non-substance-induced, preexisting lifetime depressive, anxiety, or psychotic disorders than to have MA-induced depressive, anxiety, or psychotic disorders (Salo 2011)[1] (SAMHSA, 2021 Guideline, p. 68) • Beck Depression Inventory total score greater than 20, and one or more prior suicide attempts predict the presence of a diagnosis of major depressive disorder (MDD) three years after treatment for methamphetamine dependence (Glasner-Edwards 2008)[2]
Abbreviations	**ATS**: Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Depression

Background

- For MaUD, people appear more likely to have non-substance-induced, preexisting lifetime mood disorder (MDD, NOS, Bipolar) than to have substance-induced mood disorders (N=189, 32% vs 15%) (Salo 2011)(Salo et al., 2011)

Depression: Systematic Review and Meta-Analyses

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Stimulant use	N/A	Systematic review: Hellem 2015[3] (Critically low)	**Modafinil** Effect: **Mixed results.** No effect on MA abstinence rate, but decrease in self-reported amount/frequency of MA use. Source: 2 nonrandomized single-arm trials • McGaugh 2009 (open-label nonrandomized trial, n=8 MaUD, Modafinil up to 400 mg/d, 6 wks) No effect on % positive UDS per week (t=−0.52, df=23, p=0.61) but significant decrease in self-reported MA use (mg/wk) over time (t=−2.86, df=259, p<0.005). • McElhiney 2009 (single-blind nonrandomized trial, n=13 MaUD or "MA-abusing" HIV+ men, Modafinil up to 200 mg/d + CBT, 16 weeks) 6/10 (60%) medication responders (>50% reduction in reported days used per week by the end of the study)	Review focused on co-occurring MaUD and depression
			Citicoline vs placebo Effect: **No effect** on UDS-confirmed or self-reported MA use Source: 1 double-blind RCT • Brown 2012 (double-blind RCT, n=48 MaUD with Bipolar or unipolar depression, Citicoline vs Placebo, 12 weeks) NSD between groups found in change in UDS-confirmed or self-reported MA use at the trial end or in MA use during the study.	
		Study: Afshar 2012[4]	**Mirtazapine (45 mg/d) vs Placebo** Effect: **No effect** on UDT-confirmed cocaine use Double-blind RCT, n=24 adults with co-occurring CoUD and depression (major depression, dysthymic disorder, or substance-induced mood disorder)	
		Meta-analysis: Torrens 2005[5] (Supplemental)	**Non-SSRI antidepressants vs placebo** Effect: **No effect** on reduction of cocaine consumption in 2 RCTs (14/48 vs 5/35, OR=2.32 [0.74, 7.3], p=0.15; I-squared=0%, p=0.9) • Nunes 1995 subgroup (n=69 CoUD w/ Depression, Imipramine 150-300mg/d vs Placebo, 12 weeks) NSD in % achieving at least three consecutive UDS-confirmed, cocaine-negative weeks (10/38 [26%] vs 4/31 [13%], p < 0.19).	Cocaine use disorder and Major Depressive Disorder

			• Ziedonis 1991 subgroup (n=14 cocaine "abuse" w/ Depression & OUD in MMT, Desipramine 150 mg/d vs Amantadine 300 mg/d vs Placebo, 12 weeks) Increased % of cocaine-free UDS in the last 2 weeks in desipramine or amantadine treated vs placebo patients (4/10 [42%] vs 1/4 [6%], $p < 0.01$)	
			Fluoxetine vs placebo Effect: **No effect** on reduction of cocaine consumption in 1 RCT (7/34 vs 11/34, OR=0.54 [0.18, 1.63], p=0.27) • Schmitz 2001 (n=32 CoUD w/ Depression, Fluoxetine 40mg/d + CBT vs Placebo + CBT) Fewer cocaine positive urines were found during the first 6 weeks of treatment in the placebo group compared with fluoxetine. NSD between groups in cocaine-neg UDS at the end of treatment	
Depressive symptoms	N/A	Review of reviews: Farrell 2019[6] (Supplemental)	**Antidepressants vs placebo** Effect: **Decreased** Hamilton Depression Rating Scale score MD -1.41 (-2.44--0.37) Evidence: 1 meta-analysis • Pani 2011[7] Cochrane meta-analysis of antidepressants vs placebo for **CoUD**. Co-occurring psychiatric disorders explicitly excluded in 11/37 (30%) included RCTs. o Effect: **Decreased** Hamilton Depression Rating Scale score at the end of the treatment: 6 studies, 420 participants, MD -1.41 (Cl 95% -2.44 to -0.37): ▪ Ciraulo 2005a (unclear RoB); Ciraulo 2005b (unclear RoB); Cornish 2001 (unclear RoB); Margolin 1995 (high RoB); McDowell 2005 (low RoB); Winhusen 2005 (unclear RoB). o **No effect** on CGI depression severity score at the end of the treatment: 3 studies, 390 participants, MD -0.08 (Cl 95% -0.35 to 0.18): Ciraulo 2005b (unclear RoB); Elkashef 2006 (low RoB); McDowell 2005 (unclear RoB). o "Looking at our review, partially positive results obtained by antidepressants on mood-related outcomes, which are consistent with the primary effect of antidepressants, do not seem to associate whit an effect on primary outcomes (dropout, cocaine use, side effects)." (p. 30) o "Since data available did not allow us to investigate in subgroup analysis the presence of mood depression, we cannot be conclusive on their efficacy on cocaine abuse/dependence in patients with comorbid depression." (p. 30) Review rating of evidence: **Level of evidence: A** (consistent conclusions across meta-analyses, high quality systematic reviews, or multiple randomised controlled trials)	Depressive disorder not an explicit inclusion criteria

		Systematic review: Hellem 2015[3] (Critically low)	**Antidepressants vs placebo** Effect: **No effect** on reducing depressive symptoms. "The findings consistently showed no significant changes in depressive symptoms" (p. 6) Source: 6 double-blind randomized trials, 4 placebo-controlled • Cruickshank 2008 (double-blind RCT, n=31 ATS or MA withdrawal, Mirtazapine vs Placebo, 2 weeks) No effect on Depression-Anxiety-Stress Scale; Elkashef 2008 (double-blind RCT, n=151 MaUD, Bupropion SR 150mg twice daily+CBT vs Placebo+CBT, 12 weeks) NSD in Hamilton Depression Rating Scale; Galloway 1994 (double-blind randomized trial, n=183 CoUD/MaUD, Imipramine 10, 50, 100, 150 mg, 26 weeks) NSD in Beck Depression Inventory scores; Galloway 1996 (double-blind randomized trial, n=32 MaUD, Imipramine 10 vs 150 mg, 26 weeks) NSD in Beck Depression Inventory scores; Shoptaw 2006 (double-blind RCT, n=229 MaUD or "MA-abusing", Sertraline +/-CM vs Placebo +/- CM, 12 weeks) NSD in Beck Depression Inventory scores; Shoptaw 2008 (double-blind RCT, n=73 MaUD, Bupropion SR 150mg twice daily vs Placebo, 12 weeks) NSD in Beck Depression Inventory scores	Review focused on co-occurring MaUD and depression
			Modafinil Effect: **Decreased.** "Although investigations of modafinil should be interpreted cautiously because of small, heterogeneous samples sizes, clinicians might consider prescribing it for patients with depression and MA use disorders." (p. 9) Source: 2 nonrandomized single-arm trials • McGaugh 2009 (open-label nonrandomized trial, n=8 MaUD, Modafinil up to 400 mg/d, 6 wks) Significant decrease in Hamilton Depression Rating Scale scores (t=−3.25, df=29, p=0.003) McElhiney 2009 (single-blind nonrandomized trial, n=13 MaUD or "MA-abusing" HIV+ men, Modafinil up to 200 mg/d + CBT, 16 weeks) Beck Depression Inventory score decreased −18 (SD= 8.2) in medication responders (>50% reduction in reported days used per week by the end of the study)	
			Citicoline vs placebo Effect: **Decreased** depressive symptoms in a sample of unipolar and bipolar depressed MA-using adults Source: 1 double-blind RCT • Brown 2012 (double-blind RCT, n=48 MaUD with Bipolar or unipolar depression, Citicoline vs Placebo, 12 weeks) Citicoline group experienced a 33% improvement in depression rating scores compared with a 13% improvement in the placebo group. Inventory of Depressive Symptomatology-Clinician Version.	
		Study: Afshar 2012[4]	**Mirtazapine (45 mg/d) vs placebo** Effect: **No effect** of on Hamilton Depression Rating Scale Double-blind RCT, n=24 adults with co-occurring CoUD and depression (major depression, dysthymic disorder, or substance-induced mood disorder)	

		Meta-analysis: Torrens 2005[5] (Supplemental)	**Antidepressants vs placebo** **Effect: No effect** on improvement of depressive symptoms in 2 RCTs (35/72 [48.6%] vs 24/65 [36.9%], OR 1.67 [0.74, 3.77], p=0.22; I-squared=26.6%, p=0.24) • Nunes 1995 subgroup (double-blind RCT, n=69 CoUD w/ Depression, Imipramine 150-300mg/d vs Placebo, 12 weeks) NSD on Hamilton Depression Rating Scale or Beck Depression Inventory • Schmitz 2001 (double-blind RCT, n=32 CoUD w/ Depression, Fluoxetine 40mg/d + CBT vs Placebo + CBT) NSD between groups on Hamilton Depression Rating Scale; both improved over time.	Cocaine use disorder and Major Depressive Disorder

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Depression: Included Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Afshar 2012[4]	RCT, double-blind 2-4 wk screening period, 12 wks, 8-wk follow-up USA Outpatient	(1) **Mirtazapine** (target dose 45 mg/d) (2) **Placebo** All participants received 1 hr/week manual-guided relapse prevention counseling.	N=24 adults (age 18–64) with co-occurring cocaine use disorder (DSM-IV) and depression (major depression, dysthymic disorder, or substance-induced mood disorder) with baseline HAM-D score ≥ 12.	**Cocaine use** (UDT): No sig diff between groups **Depression** (Hamilton Depression Rating Scale): No sig diff between groups **Adverse events**: No serious adverse events reported during the study. No withdrawals due to adverse events	In Chan 2019[8]

Anxiety

Background

- For MaUD, people appear more likely to have non-substance-induced, preexisting lifetime anxiety disorder (GAD, PTST, OCD, Panic disorder, Conversion disorder) than to have substance-induced anxiety disorder (N=189, 24% vs 4%) (Salo et al., 2011)

No relevant research was identified in the literature review regarding clinical effectiveness of medications for managing anxiety (substance-induced or pre-existing) in patients

Anxiety: Individual Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Afshar 2012[4]	RCT, double-blind	(1) **Mirtazapine** (target dose 45 mg/d)	N=24 adults (age 18–64) with co-occurring	**Anxiety** (HAM-A): n.s.d. between groups; decrease over time in both groups.	Chan 2019[8]: RoB High.

	2-4 wk screening period, 12 wks, 8-wk follow-up USA Outpatient	(2) **Placebo** All participants received 1 hr/week manual-guided relapse prevention counseling.	cocaine use disorder (DSM-IV) and depression (major depression, dysthymic disorder, or substance-induced mood disorder) with baseline Hamilton Depression Rating Scale (HAM-D) score of 12 or greater.	**Adverse events**: No serious adverse events reported during the study. No withdrawals due to adverse events **Other measures**: Cocaine use (no effect), Cocaine craving (favors placebo), Depression (trend for mirtazapine), Global state (trend for placebo), Sleep quality (favors mirtazapine) Condition-blind study psychiatrists rated mirtazapine group as having significantly less motivation to stop using cocaine than the placebo group on a 1-10 scale in a post	Details regarding randomization and allocation concealment not reported. High medication adherence as assessed by pill count (91%, SD 21) and urine samples (93.5%, SD 7.6).
Cruickshank 2008[9]	RCT, double-blind 2 wk medication phase 35-day follow-up Australia Outpatient	(1) **Mirtazapine** (15 mg/d for 2 days, 30 mg/d for 12 days) (2) **Placebo** All participants were offered narrative therapy counselling	N=31 amphetamine or MA-dependent (DSM-IV) adults (age 18-65) who used amphetamines in the 72 hours prior to recruitment experiencing withdrawal (63% men). 66% of participants scored above the ACSA cutoff indicating non-organic insomnia.	**Anxiety** (DASS subscale): n.s.d between groups @ either time. However, significantly higher baseline anxiety score in mirtazapine group compared to placebo (mean 23 vs 18, $p<0.05$). **Other outcomes:** Sleep (placebo favored, but mirtazapine group had better sleep at baseline). n.s.d. between groups in treatment retention, treatment duration, MA use, Dependence severity, Depression, Anxiety, Stress (trend favoring mirtazapine), Withdrawal symptoms, or psychiatric symptoms	In Siefried 2020[10] and Shoptaw 2009[11] ITT analysis Better baseline sleep but higher baseline anxiety in mirtazapine group compared to placebo
McGregor 2008[12]	Historical cohort study, open-label Data collected Aug 2003-Nov 2004 Duration typically 10 days Australia Inpatient	(1) **Mirtazapine** (60 mg/d, PM dosing) (2) **Modafinil** (400 mg/d, AM dosing) (3) **TAU** (as needed antipsychotic Pericyazine 2.5–10 mg) group did not provide information on drug effects or sleep patterns Symptomatic medications were available as-needed	N=49 adults (age 18-65) admitted for MA withdrawal (DSM-IV TR) treatment who used amphetamines within the previous 96 hours. Excluded other SUD except nicotine.	**Anxiety** (ACSA item, 0-4): Mean score over 10 days • Modafinil > TAU ($p<0.001$) • Mirtazapine > TAU ($p=0.018$) • Modafinil > Mirtazapine ($p=0.008$) **Serious adverse events:** None reported **Other outcomes:** Withdrawal severity (modafinil > mirtazapine, both better than TAU), Global state (modafinil > mirtazapine, modafinil > tau), Sleep (modafinil > mirtazapine)	In Perez-Mana 2013[13]

		(diazepam, nitrazepam, temazepam).			

DASS = Depression – Anxiety – Stress Scale

Sleep

Sleep: Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Mirtazapine					
Afshar 2012[4]	RCT, double-blind 2-4 wk screening period, 12 wks, 8-wk follow-up USA Outpatient	(1) Mirtazapine (target dose 45 mg/d) (2) Placebo All participants received 1 hr/week manual-guided relapse prevention counseling.	N=24 adults (age 18–64) with co-occurring cocaine use disorder (DSM-IV) and depression (major depression, dysthymic disorder, or substance-induced mood disorder) with baseline Hamilton Depression Rating Scale (HAM-D) score of 12 or greater.	**Sleep quality** (PSQI): Sleep latency was significantly lower in Mirtazapine than Placebo group at week 4 (p=0.008). n.s.d. b/n groups at week 8 and 12. "Analysis of item 4 on the HAM-D indicated that mirtazapine might be more effective than placebo in reducing problems related to early insomnia" (p. 7). **Sleep time** (self-reported): Trend towards more hours of sleep per night in Mirtazapine than Placebo group at week 4 (M=7.3 vs 5.9, p=0.06). **Adverse events**: No serious adverse events reported during the study. No withdrawals due to adverse events **Other measures**: Cocaine use (no effectO Anxiety, Depression, Craving, Global state	In Chan 2019[8]
Coffin 2020[14]	RCT, double-blind 24 wk medication phase, 12 wk follow-up USA Outpatient	(1) Mirtazapine 30 mg/d (2) Placebo	N=120 cisgender male (n=115) and transgender female (n=5) adults who have sex with men with MA use disorder (DSM-IV-TR) who had sex while using MA in the prior 6 months interest in reducing or stopping MA use recruited from the community (51% white). Excluding current major	**Sleep** (AIS): n.s.d. b/n groups at wk 12 (p=0.06). Mirtazapine had net reductions in insomnia severity score at wk 24 (MD= -1.4; 95% CI, 0.1-2.7; p=0.04), but not wk 36 (p=0.4). **Other outcomes**: Treatment retention (no effect), MA use (favors mirtazapine) Severity of dependence, Depression (Center for Epidemiologic Studies Depression Scale, Craving, Sexual risk behaviors	In Siefried 2020 [10] and Naji 2022[15]: Low risk of bias Low adherence: Participants who took at least 50% of their study medications at week 12 (37% vs 35%) and week

			depression or any psychiatric condition precluding safe participation		24 (22% vs 20%).
Cruickshank 2008[9]	RCT, double-blind 2 wk medication phase 35-day follow-up Australia Outpatient	(1) Mirtazapine (15 mg/d for 2 days, 30 mg/d for 12 days) (2) Placebo All participants were offered narrative therapy counselling	N=31 amphetamine or MA-dependent (DSM-IV) adults (age 18-65) who used amphetamines in the 72 hours prior to recruitment experiencing withdrawal (63% men). **66% of participants scored above the ACSA cutoff indicating non-organic insomnia.**	**Retention**: n.s.d. between groups @ day 14 (7/13 vs 9/18) or @ day 35 (4/13 vs 6/18). **Sleep** (AIS-5): Mixed evidence. • At baseline, more hours slept previous night (8 vs 5, p=0.043) in mirtazapine group compared to placebo. • Higher nocturnal awakening item score among the mirtazapine group compared to placebo @ day 14 (2.0 vs 0.9, p=0.041). • n.s.d. between groups in overall score @ day 14 (8 vs 3.8, p=0.09); improvement in both groups. • n.s.d. between groups @ 35 days **Other outcomes:** n.s.d. between groups in treatment duration, MA use, Dependence severity, Depression, Anxiety, Stress (trend favoring mirtazapine), Withdrawal symptoms, or psychiatric symptoms	In Siefried 2020[10] and Shoptaw 2009[11] ITT analysis Better baseline sleep but higher baseline anxiety score (23 vs 18, p<0.05) in mirtazapine group compared to placebo.
Modafinil					
Moosavi 2019[16]	RCT 8 wks Iran Outpatient psych hospital	(1) Modafinil (200 mg/day) for 8 weeks (2) Placebo	N=80 male patients with a confirmed diagnosis MA withdrawal	**Sleep** (ESS, PSQI): At 8 weeks, ESS decreased in the modafinil group ($p < 0.001$), but not in the placebo group ($p = 0.990$). The PSQI decreased in the modafinil group ($p < 0.001$), but not in the placebo group ($p = 0.980$). Effect size of the PSQI and ESS questionnaires was 0.52 and 0.72, respectively.	
Morgan 2010[17]	RCT, double-blind 16 days USA Inpatient	(1) Modafinil 400 mg morning-dosed (n=10) (2) Placebo (n=10) 16/20 (80%) participants also attended substance	N=20 met criteria for current cocaine dependence (DSM-IV) recruited from the community. No participant reported prior treatment for sleep	**Total sleep time**: Modafinil group had longer total sleep time than placebo at week 3. **Slow-wave sleep time**: Modafinil increased slow-wave sleep time compared to placebo. **REM sleep latency**: Modafinil group had shorter REM sleep latency than placebo at week 3.	Time abstinent from cocaine was associated with worsening of all sleep outcomes. Modafinil

		abuse therapy groups and received individual therapy (3) Health comparison participants (n=12) all male, age 30-50	problems or history consistent with a primary sleep disorder.	**Nighttime sleep latency**: Modafinil decreased nighttime sleep latency compared to placebo. **Subjective daytime sleepiness** (Stanford Sleepiness Scale, range 0-7): n.s.d. b/n groups	attenuated this effect.
Morgan 2016[18]	RCT, double-blind USA Inpatient 12 days followed by 6 wks outpatient	(1) Modafinil 400 mg/d (2) Placebo Outpatient treatment consisted of 3x/week CBT and CM (3 UDT/wk)	N=57 patients with cocaine dependence	**Sleep**: Modafinil had less sleep degradation typically associated with abstinence. Modafinil had an increase in N3 sleep time (p=0.002). The change in N3 sleep time mediated the higher rate of cocaine-negative UDTs **Other outcomes**: Cocaine use (favors modafinil)	
Mirtazapine vs Modafinil					
McGregor 2008[12]	Historical cohort study, open-label Data collected Aug 2003-Nov 2004 Duration typically 10 days Australia Inpatient	(1) Mirtazapine (60 mg/d, PM dosing) (2) Modafinil (400 mg/d, AM dosing) (3) TAU (as needed antipsychotic Pericyazine 2.5–10 mg) group did not provide information on drug effects or sleep patterns Symptomatic medications were available as-needed (diazepam, nitrazepam, temazepam).	N=49 adults (age 18-65) admitted for MA withdrawal (DSM-IV TR) treatment who used amphetamines within the previous 96 hours. Excluded other SUD except nicotine.	**Withdrawal symptoms** (ACSA items, 0-4): Mean score over 10 days • Modafinil > TAU in fatigue (p<0.001), vivid dreams (p<0.001), hypersomnia (p<0.001) • Mirtazapine > TAU in fatigue (p = .035), vivid dreams (p = 0.006) • Modafinil > Mirtazapine in fatigue (p<0.001) **Sleep** (St. Mary's Hospital Sleep Questionnaire): Modafinil group had deeper sleep compared to mirtazapine (p=0.019) and fewer nighttime awakenings (1.7 vs 2.4, p=0.01). Mirtazapine group reported significantly more hours asleep during the day (p=0.012), at night (p=0.015), and in total (p=0.002) compared to the modafinil group. Significant interaction in sleep quality (p=0.013). Effects not explained by authors. In figure, appears Modafinil group had poorer sleep quality at baseline compared to Mirtazapine. Quality improved over time in Modafinil group but declined over time in Mirtazapine group. **Serious adverse events:** None reported	In Perez-Mana 2013[13]

				Other outcomes: Withdrawal severity (modafinil > mirtazapine, both better than TAU), Global state (favors modafinil, no effect for mirtazapine)	

Existing Guidelines

Beaulieu S, Saury S, Sareen J, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. *Ann Clin Psychiatry*. 2012;24(1):38-55.

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Sleep: Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Chakravorty 2018[19]	Sleep Management Among Patients with Substance Use Disorders A referral to a sleep medicine clinic should be considered for insomnia disorder or other intrinsic sleep disorders, especially during abstinence. **Approach to the assessment of patients with sleep disorders** • Insomnia may be assessed using a structured rating instrument such as the Insomnia Severity Index (ISI) or a sleep diary. Acute insomnia denotes a recent onset of insomnia, less than 3 months in duration, and is common in the acute withdrawal phase from substances. It may be treated with reassurance, close monitoring, or with medications. most of the FDA-approved hypnotic medications such as temazepam or zolpidem may be contraindicated in patients with SUD. Insomnia comorbid with active substance use is optimally treated in a substance misuse program or primary care setting staffed by clinicians with experience in substance-related problems. In contrast, chronic insomnia in patients with remitted SUD are best treated by referral to a sleep medicine clinic o AIS = Athens Insomnia Scale • Circadian rhythm sleep disorder-delayed sleep phase type is a particular subtype of circadian rhythm sleep disorders that is characterized by going to bed later in the night and awakening later in the morning. It may be easily assessed in a clinic setting using sleep diaries, actigraphy or with the help of rating scales that evaluate the patient's propensity for sleep at a particular time during the 24-hour period. o CSM questionnaire = Composite Scale of Morningness **Cocaine and its associated sleep disorders** • Modafinil improved total sleep time and stage 3 sleep in patients with CoUD [33[	

	• Other medications with demonstrated efficacy in improving sleep continuity disturbance in individuals with cocaine use disorder: lorazepam, tiagabine and mirtazapine • Both lorazepam and tiagabine decreased sleep latency but tiagabine increased slow wave sleep in recently abstinent persons with CoUD [37]. • Mirtazapine improved sleep onset latency in depressed subjects with CoUD after 4 weeks (Afshar 2012)[4]	

Sleep: Resources from Existing Guidelines

Source	Resource	Comments
SAMHSA	In Brief: Treating Sleep Problems of People in Recovery From Substance Use Disorders (https://store.samhsa.gov/product/SMA14-4859): This publication explains how healthcare providers can help clients in recovery from SUDs who have sleep problems. It discusses the potential impact of poor sleep on recovery and offers recommendations on screening and treatment.	
DASSA	Drug and Alcohol Services South Australia (DASSA). (2022, May 6). Sleep problems—Insomnia Management Kit. https://www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Services/Mental+Health+and+Drug+and+Alcohol+Services/Drug+and+Alcohol+Services/For+health+professionals+DASSA/Sleep+problems+-+Insomnia+Management+Kit The Insomnia Management Kit is designed for GPs with patients who report sleep problems - includes assessment, diagnosis and management	
Turning Point	Why Sleep is Important, www.turningpoint.org.au/spotlights/why-does-sleep-matter	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on sx, severity Higher severity warrants	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*

	As above	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

No evidence was found regarding discontinuation of antipsychotic medications in this context; however, the CGC considered the desirable effects from protection against unnecessary exposure to and development of known adverse effects of chronic antipsychotic or mood stabilizing medications (eg, lithium, valproate).

Subgroup Considerations

None noted

Implementation Considerations

- Consider medication safety in the context of potential continued stimulant and other substance use by the patient.

Research Priorities

Research on timing and subgroup considerations in tapering

References

1. Salo R, Flower K, Kielstein A, Leamon MH, Nordahl TE, Galloway GP. Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Res*. 2011;186(2-3):356-361. doi:10.1016/j.psychres.2010.09.014
2. Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, et al. Identifying Methamphetamine Users at Risk for Major Depressive Disorder: Findings from the Methamphetamine Treatment Project at Three-Year Follow-Up. *Am J Addict*. 2008;17(2):99-102. doi:10.1080/10550490701861110
3. Hellem TL, Lundberg KJ, Renshaw PF. A review of treatment options for co-occurring methamphetamine use disorders and depression. *J Addict Nurs*. 2015;26(1):14-23; quiz E1. doi:10.1097/JAN.0000000000000058
4. Afshar M, Knapp CM, Sarid-Segal O, et al. The Efficacy of Mirtazapine in the Treatment of Cocaine Dependence with Comorbid Depression. *Am J Drug Alcohol Abuse*. 2012;38(2):181-186. doi:10/fx8sr5
5. Torrens M, Fonseca F, Mateu G, Farré M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend*. 2005;78(1):1-22. doi:10.1016/j.drugalcdep.2004.09.004
6. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
7. Pani PP, Trogu E, Vecchi S, Amato L. Antidepressants for cocaine dependence and problematic cocaine use. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online December 7, 2011. doi:10/bwcmkc
8. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for cocaine use disorder-a systematic review and Meta-analysis. *J Gen Intern Med*. 2019;34(12):2858-2873. doi:10.1007/s11606-019-05074-8
9. Cruickshank CC, Montebello ME, Dyer KR, et al. A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev*. 2008;27(3):326-333. doi:10.1080/09595230801935672
10. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
11. Shoptaw SJ, Kao U, Heinzerling K, Ling W. Treatment for amphetamine withdrawal. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online April 15, 2009. doi:10/fw8k5x
12. McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: A comparison of mirtazapine and modafinil with treatment as usual. *J Subst Abuse Treat*. 2008;35(3):334-342. doi:10.1016/j.jsat.2007.12.003
13. Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 2, 2013. doi:10/gn757q
14. Coffin PO, Santos GM, Hern J, et al. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA Psychiatry*. 2020;77(3):246-255. doi:10.1001/jamapsychiatry.2019.3655
15. Naji L, Dennis B, Rosic T, et al. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. *Drug Alcohol Depend*. 2022;232:109295. doi:10.1016/j.drugalcdep.2022.109295
16. Moosavi SM, Yazdani-Charati J, Amini F. Effects of Modafinil on Sleep Pattern during Methamphetamine Withdrawal: A Double-blind Randomized Controlled Trial. *Addict Health*. 2019;11(3). doi:10.22122/ahj.v11i3.219

17. Morgan PT, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing Effects of Modafinil on Sleep in Chronic Cocaine Users. *Am J Psychiatry*. 2010;167(3):331-340. doi:10.1176/appi.ajp.2009.09050613
18. Morgan PT, Angarita GA, Canavan S, et al. Modafinil and sleep architecture in an inpatient-outpatient treatment study of cocaine dependence. *Drug Alcohol Depend*. 2016;160:49-56. doi:10.1016/j.drugalcdep.2015.12.004
19. Chakravorty, Vandrey R, He S, Stein M. Sleep Management Among Patients with Substance Use Disorders. *Med Clin North Am*. 2018;102(4):733-743. doi:10/gdzsx4

Table 21. ADHD

Recommendation: For patients with co-occurring StUD and ADHD, clinicians should address ADHD symptoms as part of the treatment of StUD. Clinicals should consider:

a. prescribing psychostimulant medications to manage ADHD when the benefits of the medication outweigh the risks,
b. prescribing non-stimulant medications to manage ADHD when the benefits of psychostimulant medications do not outweigh the risks, and
c. behavioral approaches.

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate interventions to treat ADHD in patients with stimulant use disorder? 2. Are stimulant medications safe and effective to treat ADHD in patients with stimulant use disorder? 3. What contextual factors and implementation strategies may influence the safety and effectiveness of ADHD treatment?
Population	Patients with stimulant use disorder and ADHD
Intervention	Any intervention (behavioral or pharmacotherapy) to reduce the symptoms of ADHD
Comparison	TAU, or conditions are treated separately
Main Outcomes	StUD symptoms, ADHD symptoms, Treatment retention, Adverse events
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Notes • Co-occurring StUD & ADHD prevalence rate based on the CAADID in an international study of 1138 SUD treatment-seeking adults **22% (0.16–0.28)** (van de Glind 2013)[1] • "overall prevalence [of ADHD in SUD populations] is approximately 23%, irrespective of age and gender, ethnicity, duration of abstinence, time-frame, and setting. A series of meta-regression analyses showed that the prevalence of ADHD is significantly lower in subjects with cocaine as their primary substance of abuse" compared to alcohol dependence, opioid dependence and other addictions (van Emmerik-van Oortmerssen 2012)[2]. But CoUD populations may be older than the general SUD population. • The Conners Adult ADHD Rating Scale (CAARS) had the highest sensitivity (94%) and specificity (86%) among screening instruments used to identify ADHD among 102 adults seeking outpatient treatment for cocaine dependence in a repeated measures cohort study (Dakwar 2012)[3]. The Wender Utah Rating Scale (WURS) also performed well, and while the Adult

	ADHD Self-Report Scale Version 1.1 (ASRS-V1.1) had the weakest performance, it is the simplest and shortest instrument to administer. • In a cross-sectional study, Barkley's executive dysfunction scale showed good discriminant validity in identifying adult cocaine use disorder patients with and without ADHD (Vergara-Moragues 2011)[4]. • "Studies have shown high levels of psychiatric comorbidity (eg ...ADHD...) among chronic stimulant users (Grund et al. 2010; Fischer, Kuganesan, et al. 2015)." (Rigoni 2018, p20)[5]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **BID**: Twice per day, **CoUD**: Cocaine use disorder, **IR:** Immediate release, **MA:** Methamphetamine, **MAS-ER**: Mixed amphetamine salts extended release, **MMT**: Methadone maintenance therapy, **MPH:** Methylphenidate, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **OROS**: osmoticrelease oral system, **OUD**: Opioid use disorder, **RCT**: Randomized Control Trial, **SR**: Sustained release, **StUD**: Stimulant use disorder, **TID**: Three times per day, **UDS**: Urine drug screen
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Sustained stimulant abstinence	Moderate	Meta-analysis: Tardelli 2020[6] (High)	**No significant difference** between psychostimulants and placebo in likelihood of 2–3 weeks of sustained abstinence in 4 RCTs (n=349, p=0.63). • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg); Levin 2006 (n=93 OUD & [53%] CoUD in MMT, 12 wk, MPH SR 10-80 mg/d & Bupropion 100–400 mg/d); Levin 2007 (n=106 CoUD, 14 wk, MPH-SR max 60 mg/d); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg)	Co-occurring stimulant use disorder and ADHD
		Meta-analysis: Castells 2016[7] (Not assessed)	**No significant difference** between psychostimulant and placebo in sustained cocaine abstinence in 2 RCTs (n=232, p=0.46), but significant heterogeneity (I^2=74%, p=0.05). • Levin 2007 (n=106 CoUD, 14 wk, MPH-SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
Stimulant abstinence rate	Moderate	Systematic review: Cook 2017[8] (Moderate)	**Mixed evidence** **Psychostimulants > Placebo** in reduced stimulant use in 2 studies: • Konstenius 2014 (n=54 MaUD, 12 wk, MPH OROS 18–180 mg vs placebo) rate of drug-neg UDS 23% vs 16%, p=0.047; Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg vs 80mg vs placebo) odds of a cocaine-neg week in 60mg (OR	Co-occurring **StUD** and ADHD in adults

			2.92, p=0.02) & 80mg (OR 5.46; p<0.001). Higher end-of-tx continuous (3 wk) abstinence in 60mg & 80mg group vs placebo. **No significant difference** between psychostimulants and placebo groups in % UDS-neg in 4 studies: • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH OROS 18–72 mg/d); Levin 2006 (n=93 OUD & [53%] CoUD on MMT, 12 wk, MPH SR 10-80 mg/d & Bupropion 100–400 mg/d); Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	
		Meta-analysis: Castells 2016[7] (Not assessed)	**No significant difference** between psychostimulant and placebo in mean proportion of cocaine-free urinalyses across the study per patient in 2 RCTs (n=154, p=0.94). • Levin 2007 (n=106 CoUD, 14 wk, MPH-SR 40-60 mg/d BID); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No significant difference** between psychostimulants vs placebo in UDT-confirmed amphetamine use in 1 RCT (p=0.61) • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD
Treatment completion	Moderate	Meta-analysis: Castells 2016[7] (Not assessed)	**No significant difference** between psychostimulant and placebo in 3 RCTs (p=0.64). 1. Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No significant difference** between psychostimulants vs placebo in treatment retention in 1 RCT (p=0.2) • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD
Serious adverse events	Moderate	Meta-analysis: Castells 2016[7] (Not assessed)	**No serious adverse events** reported in 3 RCTs (n=280) 2. Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No serious adverse events** reported in 1 RCT (n=24) • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD

Dropout due to cardiovascular adverse events	Moderate	Meta-analysis: Castells 2016[7] (Not assessed)	**No significant difference** between psychostimulant and placebo in rate of dropouts due to cardiovascular adverse events in 3 RCTs (n=280, 0/160 [0.0%] vs 1/120 [0.8%], p=0.7). 3. Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No dropouts** due to cardiovascular adverse events reported in 1 RCT • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD
Dropout due to psychiatric adverse events	Moderate	Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No significant difference** between psychostimulants and placebo in dropouts due to psychiatric adverse events in 1 RCT (n=24, 1/12 [8.3%] vs 0/12 [0%], p=0.42) • Konstenius 2010 (n=24 ATStUD, 12 wk, MPH-SR 18–72 mg)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD
Important Outcomes				
ADHD symptoms	N/A	Systematic review: Zaso 2020[10] (Not assessed)	Extended-release formulations of methylphenidate **MPH-OROS > Placebo** in reduced ADHD symptoms • Riggs 2011 (n=303 SUD, MPH-OROS 72 mg/d) **MPH-SODAS > Placebo in** improved ADHD symptoms • Szobot 2008 (n=16 cannabis or CoUD, MPH-SODAS 1.2 mg/kg/d) Nonstimulant medications **No significant difference** between atomoxetine and placebo in ADHD symptoms: • Thurstone 2010 (n=70 SUD, Atomoxetine >70 kg 50 to 100 mg/d) **Bupropion** decreased ADHD symptoms in two small non-randomized trials: • Riggs 1998 (n=13 SUD, BUP 300 mg/d); Solhkah 2005 (n=14 SUD, BUP SR ave 250 mg/d)	Co-occurring **substance use disorder (SUD)** and ADHD in adolescents
		Systematic review: Cook 2017[8] (Moderate)	**Mixed evidence** for adults with co-occurring stimulant use disorder and ADHD: **Psychostimulants > Placebo** in improved ADHD outcome measures in 4 studies: • Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Ginsberg & Lindefors 2012 (n=30 ATStUD/CoUD, 5 wk, MPH OROS 36–72 mg); Konstenius 2014 (n=54 MaUD, 12 wk, MPH OROS 18–180 mg/d); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID) **No significant difference** between methylphenidate and placebo in ADHD outcome measures in 4 studies. • Carpentier 2005 (n=25 [56%] CoUD, 8 wk, MPH 15-46 mg/d); Konstenius 2010 (n=24 ATStUD, 12 wk, MPH OROS 18–72 mg/d); Levin 2006 (n=93	Managing ADHD in adults using illicit psychostimulants

			OUD & [53%] CoUD on MMT, 12 wk, MPH SR 10-80 mg/d & Bupropion 100–400 mg/d); Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID) **No significant difference** between bupropion and placebo in ADHD outcome measures in 1 study: • Levin 2006 (n=93 OUD & [53%] CoUD on MMT, 12 wk, MPH SR 10-80 mg/d & Bupropion 100–400 mg/d)	
		Meta-analysis: Castells 2016[7] (Not assessed)	**Trend for psychostimulant** group to have greater improvements in ADHD symptom severity compared to placebo in 3 RCTs (n=247, OR -0.41, 95%CI -0.83 to 0.01, p=0.06). • Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Cunill 2015[11] (Not assessed)	**No significant difference** between pharmacotherapy and placebo on ADHD symptom severity (p=0.699). • Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID); Konstenius 2010 (n=24 ATStUD, 12 wk, MPH OROS 18–72 mg/d)	This may be a partial list of studies. Can't access supplementary material on publisher's website.
SUD symptoms	N/A	Systematic review: Zaso 2020[10] (Not assessed)	Extended-release formulations of methylphenidate **MPH-OROS > Placebo in** reducing some SUD symptoms • Riggs 2011 (n=303 SUD, MPH-OROS 72 mg/d) **No significant difference** between MPH-SODAS and placebo in improving SUD symptoms • Szobot 2008 (n=16 cannabis or CoUD, MPH-SODAS 1.2 mg/kg/d) Nonstimulant medications **No sig difference** between atomoxetine and placebo in SUD symptoms: • Thurstone 2010 (n=70 SUD, Atomoxetine >70 kg 50 to 100 mg/d) **Bupropion** decreased SUD symptoms in a small non-randomized trial • Solhkah 2005 (n=14 SUD, BUP SR ave 250 mg/d)	Co-occurring **substance use disorder (SUD)** and ADHD in adolescents
Adverse event	N/A	Systematic review: Cook 2017[8] (Moderate)	Extended-release mixed amphetamine salts (1 study) • Dry mouth occurred significantly more frequently compared with placebo (Levin et al., 2015) Methylphenidate (7 studies) • "Generally of mild–moderate severity (Konstenius et al., 2014; Levin et al., 2015), except for one event of blurred vision (Konstenius et al., 2010) and two severe events of hypertension and disorientation, both of which resolved with a reduction in dose (Schubiner et al., 2002)." Bupropion (1 study)	Managing ADHD in adults using illicit psychostimulants

			• No significant adverse effects reported (Levin et al., 2006)	
		Meta-analysis: Castells 2016[7] (Not assessed)	**No significant difference** between psychostimulant and placebo in rate of dropout (%n) due to any adverse events in 3 RCTs (n=280, 1/160 [0.6%] vs 2/120 [1.7%], p=0.84). 4. Levin 2007 (n=106 CoUD, 14 wk, MPH SR 40-60 mg/d BID); Levin 2015 (n=126 CoUD, 13 wk, MAS-ER 60mg & 80mg); Schubiner 2002 (n=43 CoUD, 12 wk, MPH IR 30-90 mg/d TID)	Cochrane review of psychostimulants for **CoUD**; sub-analysis for comorbid ADHD
		Meta-analysis: Perez-Mana 2013[9] (Not assessed)	**No significant difference** between psychostimulants vs placebo in dropouts due to adverse events in 1 RCT (p=0.42)	Cochrane review of psychostimulants for **ATStUD**; sub-analysis for comorbid ADHD

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Manni 2019[12]	Non-random Cohort study 1-30 months (mean=7) Italy Outpatient adult ADHD clinic	(1) Methylphenidate (MPH): treated with IR max dose 60 mg/day or ER standard dose 60–90 mg/day (2) Atomoxetine (ATM): treated with standard dose 1.2 mg/kg/day	N=20 adults with cocaine use disorder and first diagnosis of ADHD in adulthood. Excluded current psychotic symptoms and cardiovascular comorbidities. All patients met the psychiatric comorbidity criteria for bipolar 1 disorder.	**Cocaine use**: n.s.d. between groups **CoUD symptoms** (Cocaine Problem Severity Index, CPSI): n.s.d. between groups **ADHD symptoms** (A-ADHD Self-Report Scale, ASRS-v1.1): n.s.d. between groups **Clinical Global Impression** (CGI): n.s.d. between groups CUD improvement over time was closely correlated with ADHD symptom improvement.	Also in EtDT Adol ADHD Treatment
van Emmerik-van Oortmerssen 2019[13]	RCT 2 month follow-up Netherlands Outpatient	(1) **Integrated CBT for SUD & ADHD**: 15 individual sessions of motivational therapy, coping skills training and relapse prevention for SUD, and training of planning skills, problem-solving skills	N=119 treatment-seeking adults with ADHD and SUD other than nicotine (primary substance of abuse stimulants, n=28, 23.5%). 5 participants already on ADHD medication at the start of the trial were asked	**ADHD symptom severity** (ARS): Integrated CBT had lower scores at the end of treatment (M[sd] 28.1 [9.0] vs 31.5 [11.4], F=4.739, df = 1, 282, p=0.030; d=0.34). n.s.d. at 2-month follow-up (p=0.076). **Other outcomes**: n.s.d. in substance use (TLFB self-report), Depressive	

		and dealing with emotions for ADHD. (2) **CBT**: 10 individual SUD treatment sessions only	to maintain dose, but patients did not start medication during the trial. Patients with (a history of) severe neurological (eg, dementia, Parkinson's disease), severe psychiatric disorders (eg, psychosis, bipolar disorder), borderline personality disorder were excluded	symptoms (BDI), Anxiety symptoms (BAI), Quality of life (BQ-5D)	

ARS = ADHD Rating Scale; TLFB = Time Line Follow Back; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

Existing Guidelines

Özgen H, Spijkerman R, Noack M, et al. International Consensus Statement for the Screening, Diagnosis, and Treatment of Adolescents with Concurrent Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder. *Eur Addict Res*. 2020;26(Suppl. 4-5):223-232. doi:10.1159/000508385

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Chamakalayil 2020[14]	Chamakalayil S, Strasser J, Vogel M, Brand S, Walter M, Dürsteler KM. Methylphenidate for Attention-Deficit and Hyperactivity Disorder in Adult Patients With Substance Use Disorders: Good Clinical Practice. *Front Psychiatry*. 2020;11:540837. doi:10.3389/fpsyt.2020.540837	Not stimulant-specific
Jensen & Breindahl 2019[15]		
Sullivan & Rudnik-Levin 2006[16]	Attention Deficit/Hyperactivity Disorder and Substance Abuse • "Patients with ADHD encounter particular difficulties when they enter a standard setting for substance-abuse treatment. These include their diminished ability to process new information (which persists when they are sober), inattention or distractibility in a group setting, greater likelihood to act impulsively and return to drug use, and feelings of social isolation and being misunderstood by other group members." (p. 263) • "In order for substance-abuse treatment to succeed in patients with co-morbid ADHD, modified approaches should be considered, including recognition of concomitant ADHD, psychoeducation about ADHD	

	symptoms for group leaders and participants, and earlier application of relapse-prevention techniques." (p. 264)	

Other Resources

Source	Resource	Comments
	Substance Abuse and Mental Health Services Administration. (2020l). Substance use disorder treatment for people with co-occurring disorders. Treatment Improvement Protocol (TIP) Series 42. SAMHSA Publication No. PEP20-02-01-004. Substance Abuse and Mental Health Services Administration.	
	Substance Abuse and Mental Health Services Administration. (2020n, August 19). Co-occurring disorders and other health conditions. https:// www.samhsa.gov/medication-assisted-treatment/ medications-counseling-related-conditions/ co-occurring-disorders	
	Mariani JJ Levin FR. Treatment strategies for co-occurring ADHD and substance use disorders. *Am J Addict*. 2007;16(Suppl 1):45–54; quiz 55–56. https://doi.org/10.1080/10550490601082783	
	Harstad E, Levy S, Committee on Substance Abuse, et al. Attention-Deficit/Hyperactivity Disorder and Substance Abuse. *Pediatrics*. 2014;134(1):e293-e301. doi:10.1542/peds.2014-0992	
	Hogue A, Evans SW, Levin FR. A Clinician's Guide to Co-occurring ADHD Among Adolescent Substance Users: Comorbidity, Neurodevelopmental Risk, and Evidence-Based Treatment Options. *J Child Adolesc Subst Abuse*. 2017;26(4):277-292. doi:10.1080/1067828X.2017.1305930	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence generally supports use of psychostimulants to treat ADHD in individuals with co-occurring stimulant use disorder. Some, but not all studies have demonstrated significant reduction in ADHD symptoms associated with stimulant prescription in individuals with stimulant use disorder. The majority of studies have demonstrated no significant difference in stimulant use or abstinence between individuals treated with prescription stimulants vs. placebo. Limited studies show mixed effects for non-stimulant medications atomoxetine and bupropion.	Prescription stimulants are controlled medications, and are associated with risk of development of tolerance and/or use disorder. Individuals with StUD may require higher doses of prescribed stimulant medication. Behavioral interventions for ADHD may be readily combined with pharmacotherapy treatments.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Studies have not demonstrated a difference in significant adverse effects, treatment dropout or completion between individuals with StUD (cocaine and methamphetamine) and co-occurring ADHD treated with prescription stimulants vs placebo.	Therapeutic doses of psychostimulants used to treat ADHD may increase the adverse effects of use of stimulant drugs like cocaine and MA. Prescription stimulants are controlled medications, and are associated with risk of development of tolerance and/or use disorder. However, risk mitigation strategies may be utilized. Use of non-stimulant medications for the treatment of ADHD in individuals with StUD, including off-label options that may be considered (eg atomoxetine, clonidine, bupropion), particularly for individuals with known history of prescription StUD. Pre-existing hypertension, cardiovascular disease, psychosis may prompt greater caution in using psychostimulants to treat ADHD in StUD. Also should have caution for patients with insomnia and anxiety, although somewhat less due to comparatively less severe negative outcomes.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Although evidence is mixed, some studies demonstrate beneficial effects of stimulant medication in the treatment of ADHD in individuals with StUD.	Prescription stimulants carry risk of misuse and development of stimulant use disorder. However, evidence from clinical trials to date do not demonstrate significant risk of prescription stimulant misuse over placebo. Long-term use in traditional clinical settings has not been examined, however.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
The majority of studies have demonstrated either beneficial trends or nonsignificant differences between prescription stimulants and placebo.	Study design may have contributed to insignificant differences in findings (eg underpowered, short duration, dosing ranges).	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low

		☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients and treating clinicians may place different weight on reducing StUD and ADHD outcomes. For example, from a risk perspective, clinicians may more heavily weight reducing StUD compared to ADHD symptoms.	☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	This intervention is likely implemented by specialists, and some individuals may not have access to specialist resources (eg, rural).	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Use of controlled prescription stimulants to treat ADHD in individuals remains controversial due to risk of medication misuse and/or development of use disorder.	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Integration of treatment requires certain knowledge/skill of the clinician and/or availability of specialty care/resources which may not be available in all settings.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusions

Justification

Study findings have been mixed in effects of prescription stimulants on ADHD outcomes in individuals with StUD, with some studies reporting significant differences between Rx stimulants and placebo, others with beneficial trends in effects, and others demonstrating no significant differences between medication and placebo arms. The majority of studies have examined ADHD symptoms as a secondary outcome within studies designed to evaluate stimulant use as a primary outcome. There have been limited prospective studies evaluating ADHD symptoms among individuals with StUD and co-occurring ADHD. Existing studies have not demonstrated significant adverse events, including effects on retention or dropout, when prescribing stimulants to individuals with StUD.

Subgroup Considerations

None noted

Implementation Considerations

It is important to have measures in place for risk mitigation, including checking of PDMP and UDS. Clinicians may also mitigate risk through monitoring procedures (eg checking PDMP, UDS, pill counts, increasing frequency of visits).
If prescribing a stimulant medication, monitor for adverse effects including BP and other cardiac outcomes.

Research Priorities

More research is needed to study treatment of ADHD in individuals with stimulant use disorder.

References

1. van de Glind G, van den Brink W, Koeter MWJ, et al. Validity of the Adult ADHD Self-Report Scale (ASRS) as a screener for adult ADHD in treatment seeking substance use disorder patients. *Drug Alcohol Depend*. 2013;132(3):587-596. doi:10.1016/j.drugalcdep.2013.04.010
2. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. *Drug Alcohol Depend*. 2012;122(1-2):11-19. doi:10.1016/j.drugalcdep.2011.12.007
3. Dakwar E, Mahony A, Pavlicova M, et al. The Utility of Attention-Deficit/Hyperactivity Disorder Screening Instruments in Individuals Seeking Treatment for Substance Use Disorders. *J Clin Psychiatry*. 2012;73(11):e1372-e1378. doi:10/f446nn
4. Vergara-Moragues E, González-Saiz F, Lozano Rojas O, et al. Diagnosing adult attention deficit/hyperactivity disorder in patients with cocaine dependence: discriminant validity of Barkley executive dysfunction symptoms. *Eur Addict Res*. 2011;17(6):279-284. doi:10/c7cp3n
5. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
6. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2020;237(8):2233-2255. doi:10/ghxt5x
7. Castells X, Cunill R, Pérez-Mañá C, Vidal X, Capellà D. Psychostimulant drugs for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online September 27, 2016. doi:10/f9dtms
8. Cook J, Lloyd-Jones M, Arunogiri S, Ogden E, Bonomo Y. Managing attention deficit hyperactivity disorder in adults using illicit psychostimulants: A systematic review. *Aust N Z J Psychiatry*. 2017;51(9):876-885. doi:10.1177/0004867417714878
9. Perez-Mana C, Castells X, Torrens M, Capella D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. *Cochrane Database Syst Rev*. Published online 2013. doi:10.1002/14651858.CD009695.pub2
10. Zaso MJ, Park A, Antshel KM. Treatments for Adolescents With Comorbid ADHD and Substance Use Disorder: A Systematic Review. *J Atten Disord*. 2020;24(9):1215-1226. doi:10.1177/1087054715569280

11. Cunill R, Castells X, Tobias A, Capellà D. Pharmacological treatment of attention deficit hyperactivity disorder with co-morbid drug dependence. *J Psychopharmacol Oxf Engl*. 2015;29(1):15-23. doi:10/ggw9st
12. Manni C, Cipollone G, Pallucchini A, Maremmani AGI, Perugi G, Maremmani I. Remarkable Reduction of Cocaine Use in Dual Disorder (Adult Attention Deficit Hyperactive Disorder/Cocaine Use Disorder) Patients Treated with Medications for ADHD. *Int J Environ Res Public Health*. 2019;16(20):3911. doi:10.3390/ijerph16203911
13. van Emmerik-van Oortmerssen K, Vedel E, Kramer FJ, et al. Integrated cognitive behavioral therapy for ADHD in adult substance use disorder patients: Results of a randomized clinical trial. *Drug Alcohol Depend*. 2019;197:28-36. doi:10.1016/j.drugalcdep.2018.12.023
14. Chamakalayil S, Strasser J, Vogel M, Brand S, Walter M, Dürsteler KM. Methylphenidate for Attention-Deficit and Hyperactivity Disorder in Adult Patients With Substance Use Disorders: Good Clinical Practice. *Front Psychiatry*. 2020;11:540837. doi:10.3389/fpsyt.2020.540837
15. Jensen C, Breindahl T. Patients in medical treatment for attention deficit/hyperactivity disorder (ADHD): Are they at risk in drug screening? *Atten Deficit Hyperact Disord*. 2019;11(3):333-340. doi:10/gjp7wf
16. Sullivan MA, Rudnik-Levin F. Attention Deficit/Hyperactivity Disorder and Substance Abuse: Diagnostic and Therapeutic Considerations. *Ann N Y Acad Sci*. 2006;931(1):251-270. doi:10.1111/j.1749-6632.2001.tb05783.x

Adolescents and Young Adults

Table 22. Contingency Management

Recommendation: When treating adolescents and young adults for StUD, clinicians should consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents (eg, **CM,** CBT, CRA, Family Therapy) and in the treatment of StUDs in adults (eg, **CM,** CBT, CRA).

Clinical Question Summary

Clinical Question	1. Is Contingency Management (CM) for patients with stimulant use disorder as effective and appropriate adolescents and young adults with as it is for adults? 2. What contextual factors and implementation strategies may influence the effects of CM for adolescents and young adults? 3. What modifications should be made so that CM is delivered in a developmentally appropriate manner?
Population	Adolescent (age 12-17) and young adult (age 18-25) patients with stimulant use disorder
Intervention	Contingency Management (CM) for stimulant use with or without a background treatment
Main Outcomes	Stimulant use, substance use, treatment retention, treatment attendance
Comparison	TAU
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Adolescent: age 12-17 Young adult: age 18-25 • Contingency Management is effective in adults • Why would we expect or not expect it to be differently effective, eg, different benefits, different risks, different patient values? • What types of providers/programs provide or could provide CM?
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MET**: Motivational Enhancement Therapy, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Treatment retention	Low	Systematic review: Dalton 2021[1] (Not assessed)	Favors behavioral therapy such as CBT and CM for cannabis and alcohol use disorders for adolescents and emerging adults (age 18–25). • **CM > no CM** in retention rate for cannabis use disorder @ 2 months (62.9% vs 50.7%, d=0.47, 95% CI 0.12-0.81) in 1 RCT • Carroll 2006[2] (n=136 age 18-25 Cannabis use disorder, CM+CBT/MET vs CBT/MET vs CM+Drug Counseling vs Drug Counseling)	Not stimulant specific
Important Outcomes				
Cumulative level of support	N/A	Systematic review: Hogue 2018[3] (Not assessed)	No studies of CM alone included, but CM in combination with another treatment were labeled "**well-established or probably efficacious" (p. 1)** outpatient treatments for adolescent SUD: • CM + Ecological behavioral family-based treatment evidence: o Hogue 2014 systematic review; Letourneau et al. (2017): Equivalent to TAU for AOD use • CM + CBT/MET evidence: o Stanger 2015[4] Cannabis use disorder: Superior to CBT/MET during CM period, but NSD at 1-year follow-up. CM was 3 months of continuing care following treatment. • CM + CBT/MET + behavioral family-based treatment evidence: o Stanger 2015[4]: Cannabis use disorder: Superior to CBT/MET during CM period, but NSD at 1-year follow-up. NSD from CBT/MET + CM (Family had no additional effect). CM was 3 months of continuing care following treatment; Hogue 2014 systematic review	Not stimulant specific Level of Support based on Journal of Clinical Child and Adolescent Psychology (JCCAP) criteria
Substance use	N/A	Systematic review: Steele 2020[5] (Not assessed)	In some studies, interventions (CBT, CBT+MI, CM+CBT+MI) were associated with **increased** cannabis use (Strength of evidence: Low. (p. 8)	Adolescent SUD, Not stimulant specific
		Meta-analysis: Tanner-Smith 2016[6] (Not assessed)	• **CM more effective than TAU**, Group/mixed counseling, Psychoeducational therapy, Pharmacology, Self-help • CM showed only modest differences from Assertive Continuing Care, Behavioral therapy, CBT, MET, Family therapy	Adolescent SUD, Not stimulant specific. Meta-regression analysis calculated effect size (Hedges g) to index the

			• "Overall, the mean effect sizes [of CM] relative to practice as usual are in the 0.15–0.25 range. Using Cohen's U3 index, these effects translate into a 5% to 10% improvement relative to participants in the comparison conditions. Using the results from the comparison conditions in studies reporting the number of days youth consumed marijuana in the past month, an effect size of 0.25 translates into a reduction from an average of 9.7 days in the past month to 7.2 days in the past month—a 25% reduction. " (p 11)	effects of post-treatment differences in substance use.

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Comments
Carroll 2006[2]	RCT 8 weeks 6 month follow-up USA Outpatient	**(1) CM+CBT/MET:** incentives contingent on session attendance or marijuana-neg UDS plus weekly individual motivational/ skills-building intervention **(2) CBT/MET** alone **(3) CM+DC**: CM plus weekly individual drug counseling **(4) DC** alone	N = 136 early adults (age 18–25) with a **marijuana use disorder** (DSM-IV) referral to treatment by the **criminal justice system** (90% male).	**Follow-up:** 108/136 (79.4%) @ 6 months **Treatment completion** (%n): 79/136 (60%) overall. CM+CBT/MET (23/33, 69.7%), CBT/MET alone (22/36, 63.7%), CM+DC (21/34, 66.7%), DC alone (13/33, 39.4%) • CM > no CM (62.9% vs 50.7%, d=0.47, 95% CI 0.12-0.81) • CBT/MET > DC (n=136, 65.2% vs 50.7%, $\chi 2(1)=3.8$, p=.05) **Attendance:** Number of sessions attended (mean, se) CM+CBT/MET (6.0, 0.44), CBT/MET (4.9, 0.41), CM+DC (5.4, 0.4), DC (4.2, 0.43) • CM > no CM (n=136, t(1,131)=2.72 • Significant interaction where CM+CBT/MET > CBT/MET alone OR CM+DC > DC alone (n=136, t(1,131)=2.19 **Continuous marijuana abstinence** (UDS-) Longest duration (in days) during treatment (mean, se): CM+CBT/MET (27.3, 3.6), CBT/MET alone (21.5, 3.58), CM+DC (26.4, 3.6), DC alone (17.3, 4.83)	In Dalton 2021[1] Quality score: Good High attrition (40%) Unknown if interventions were modified for early adult unique needs

				• CM > no CM: n=129, t(124)=2.1, p=.04, d=0.45 • No CBT/MET vs DC effect or interaction **Marijuana abstinence rate during treatment** (%UDS-, se): CM+CBT/MET (50%, 7%), CBT/MET (30%, 7%), CM+DC (30%, 10%), DC (30%, 7%) • Significant interaction where CM+CBT/MET > CBT/MET alone OR CM+DC > DC alone (n=132, t(127)=2.24, p<.05, d=0.28, 95% CI −0.12 to 0.67) **Weekly marijuana use rate during treatment (%UDS+):** Likelihood of submitting marijuana-positive sample during treatment • Main effect of time where likelihood decreased over time for the whole sample (z= −6.23, p<.05). • Significant interaction where likelihood was lower in CM+CBT/MET compared to other groups (z= −1.99, p<.05) **Marijuana abstinence @ follow-up (% UDS-):** NSD between groups in proportion who provided marijuana-neg sample @ 3 months and @ 6 months. **Marijuana use frequency @ follow-up (self-report TLFB):** Frequency (in days) of use • No main effect of time (no change from end of tx to 6 mo f/u) or CM vs no CM • Significant interaction of CBT/MET vs DC by time, where CBT/MET decreased frequency of marijuana use over time compared with DC (z= −2.3, p=.02). **Treatment success rate** (%n): "Clinically significant improvement was defined as (a) completing treatment… and (b) submission of at least one marijuana-free urine specimen during treatment (indicative of attaining at least 14 days of abstinence)" (p. 9) 46% CM+CBT/MET, 31% CBT/MET alone, 44% CM+DC, 21% DC alone	

				• Main effect of CM > no CM, z = 2.03, p < .05) **Other outcomes:** total consecutive marijuana-neg samples, total marijuana-neg samples, ASI	
Stanger 2015[4]	Cross-sectional USA 24 weeks	Clinic-based CM Home-based CM	Adolescents with cannabis use disorders	Post-hoc analysis showing that youth with disruptive behavior disorder diagnoses (DBD) in addition to cannabis use disorder had better outcomes when they received CM. CM strategies can be effective for retaining youth in treatment, increasing treatment attendance, and promoting abstinence across multiple types of substance use problems.	In Hogue 2018[3]

ASI = Addiction Severity Index

OR = odds ratio

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
CM in combination with other behavioral health interventions has been shown to have a small effect on reducing adolescent cannabis use and increasing treatment retention compared to behavioral health interventions alone. See ETDT Behavioral CM for effects in adults with StUD: CM consistently produced longer durations of continuous abstinence and lower rates of stimulant use than NCR (placebo) and TAU. These effects were strongest during the trials and appeared to decrease gradually over post-treatment follow-ups.	Although no direct evidence, given the effectiveness of CM in adults with StUD, the CGC also expects CM to be effective in adolescents with StUD. They are similarly motivated by rewards. The size of the desirable effect also depends on the type and magnitude of the incentive. There is a chance that vouchers or cash incentives may be more or less rewarding in adolescents and YA compared to the general adult population. Assuming that vouchers and cash are as appealing to adolescents as for adults, the effects are expected to be large, but this has not been studied.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	None expected	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		

Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Although no direct evidence, given the effectiveness of CM in adults with StUD, the CGC also expects CM to be effective in adolescents with StUD. They are similarly motivated by rewards.

Subgroup Considerations

None noted

Implementation Considerations

What modifications should be made so that CM is delivered in a developmentally appropriate manner?

- CM uses toxicology test results to identify positive behaviors
    - An adolescent patient may be hesitant to participate in CM as part of StUD treatment because they do not want parents to be informed of positive result. However,

    - Participation in urine toxicology as a part of StUD is voluntary unless court-mandated.
        - State laws vary regarding confidentiality and parental notification of treatment progress
        - Clinicians can work with parents so that positive results are not met with punitive outcomes, in accordance with the principle of CM to reinforce targeted behaviors rather than punish.
- Parents can supplement CM as part of StUD treatment by offering additional or different developmentally appropriate incentives. For some patients, engaging in prosocial behaviors such as permission to attend events or spend time with friends may be more incentivizing than cash or voucher rewards.
- Be mindful of the psychosocial context of the patient when considering reward type and magnitude.

References

1. Dalton K, Bishop L, Darcy S. Investigating interventions that lead to the highest treatment retention for emerging adults with substance use disorder: A systematic review. *Addict Behav*. 2021;122:107005. doi:10.1016/j.addbeh.2021.107005
2. Carroll KM, Easton CJ, Nich C, et al. The use of contingency management and motivational/skills-building therapy to treat young adults with marijuana dependence. *J Consult Clin Psychol*. 2006;74(5):955-966. doi:10.1037/0022-006X.74.5.955
3. Hogue A, Henderson CE, Becker SJ, Knight DK. Evidence Base on Outpatient Behavioral Treatments for Adolescent Substance Use, 2014-2017: Outcomes, Treatment Delivery, and Promising Horizons. *J Clin Child Adolesc Psychol*. 2018;47(4):499-526. doi:10.1080/15374416.2018.1466307
4. Stanger C, Ryan SR, Scherer EA, Norton GE, Budney AJ. Clinic- and Home-Based Contingency Management Plus Parent Training for Adolescent Cannabis Use Disorders. *J Am Acad Child Adolesc Psychiatry*. 2015;54(6):445-453.e2. doi:10.1016/j.jaac.2015.02.009
5. Steele DW, Becker SJ, Danko KJ, et al. *Interventions for Substance Use Disorders in Adolescents: A Systematic Review*. Agency for Healthcare Research and Quality (US); 2020. Accessed May 23, 2022. http://www.ncbi.nlm.nih.gov/books/NBK557291/
6. Tanner-Smith EE, Steinka-Fry KT, Kettrey HH, Lipsey MW. *Adolescent Substance Use Treatment Effectiveness: A Systematic Review and Meta-Analysis*. Peabody Research Institute, Vanderbilt University; 2016:76.

Table 23. Other Psychotherapy

Recommendation: When treating adolescents and young adults for StUD, clinicians should consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents (eg, CM, **CBT, CRA,** Family Therapy) and in the treatment of StUDs in adults (eg, CM, **CBT, CRA**).

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate psychotherapy interventions for the treatment of stimulant use disorder in adolescent and young adult patients? 2. What contextual factors and implementation strategies may influence the effects of psychotherapy interventions?
Population	Adolescent (age 12-17) and young adult (age 18-25) patients with stimulant use disorder
Intervention	Any psychotherapy used to treat adolescent SUD or adult StUD (except Contingency Management and Family Therapy unless adjunct; see EtDTs Adolescent CM and Adolescent Family Therapy)
Comparison	TAU
Main Outcomes	Stimulant use, substance use, treatment retention, treatment attendance
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Notes • Types of providers that provide family therapy, CBT, or other modalities, such as whether the provider was a licensed clinical social worker, licensed professional counselor, licensed clinical psychologist, psychiatrist, or other staff.
Abbreviations	**ATS**: Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CBT**: Cognitive Behavioral Therapy, **CM**: Contingency Management, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **MET**: Motivational Enhancement Therapy, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized control trial, **StUD**: Stimulant use disorder, **SUD**: Substance use disorder, **TAU**: Treatment as usual, **UDS**: Urine drug screen, **UDT**: Urine drug test
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Note: Contingency Management and Family Therapy studies (unless adjunct to another psychotherapy) are in their own ETD Tables.

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				

Treatment retention	N/A	Systematic review: Dalton 2021[1] (Not assessed)	Favors behavioral therapy such as CBT and CM for cannabis and/or alcohol use disorders • Carroll 2006 (n=135 age 18-25 Cannabis use disorder, MET/CBT+CM vs MET/CBT vs Drug Counseling + CM vs Drug Counseling) retention @ 2 mo 70%, 67%, 64%, 40% respectively • Esposito-Smythers 2013 (n=17 age 18-24 Alcohol &/or cannabis use disorder w/ HIV, CBT+CM) retention @ 4 mo 82% • Smith 2015 (n=35 age 18-25 SUD, CRA) retention @ 3 mo 11%	Adolescents and emerging adults (age 18–25). Not stimulant specific
Important Outcomes				
Substance use	N/A	Meta-analysis: Steele 2020[2] (Not assessed)	• **CBT** reduced days of combined alcohol and other drug use relative to TAU (Strength of evidence: Low) (p. 8) • **CBT+MI** reduces days of illicit drug use relative to TAU (Strength of evidence: Low, Indirect)" (p. 52) • CBT did not decrease cannabis use. In some studies, interventions (CBT, CBT+MI, and CBT+MI+CM) were associated with increased cannabis use (Strength of evidence: Low) (p. 8)	Adolescent SUD, Not stimulant specific

		Meta-analysis: Tanner-Smith 2016[3] (Not assessed)	Change in substance use: Pre-Post after intake, effect size [95% CI]
			• "Across all the 380 pre–post substance use effect sizes, the random effects mean was 0.54 ($p < .001$; 95% CI [0.38, 0.71]), indicating that adolescents exhibited significant decreases in their substance use after entry into treatment. The mean reductions were greatest for **mixed substance use** ($g\bar{g} = 0.63$, $p < .001$, 95% CI [0.42, 0.84]) and **marijuana use** ($g\bar{g} = 0.36$, $p = .006$, 95% CI [0.13, 0.58]). The mean reductions were nonsignificant for **alcohol** ($g\bar{g} = 0.22$, $p = .06$, 95% CI [-0.01, 0.45]) and **other specific (eg, cocaine) substance use** ($g\bar{g} = 0.42$, $p = .08$, 95% CI [-0.26, 1.09]). There was evidence of substantial heterogeneity in the pretest–posttest effect sizes ($\chi 2 = 568.81$, $p < .001$, $\tau 2 = 0.25$; $I^2 = 50.08\%$), indicating that differences across the arms influence the magnitude of adolescents' reductions in substance use after entry into treatment." (p. 11)
			• "The largest reductions were observed for **MET/CBT**, family therapy, and **CBT** programs." (p. 1)
			  ○ **CBT**: 10 studies, Hedges g=1.15 [0.89, 1.42]
			  ○ **MET/CBT**: 8 studies, Hedges g=1.12 [0.81, 1.43]
			  ○ TAU: 11 studies, Hedges g=0.86 [0.61, 1.11]
			  ○ No treatment: 8 studies, Hedges g=0.96 [0.74, 1.18]
			Comparative treatment effectiveness: Mean group posttest comparison, effect size [95% CI]
			• "Assertive continuing care (ACC), behavioral therapy, CBT, MET, family therapy: These treatment modalities tend to be more effective than [MET/CBT, TAU, No
				Adolescent SUD, Not stimulant specific.
				
				Note, results of the 2 analyses not fully comparable, mostly from missing baselines in Pre-Post analysis.
				
				Comparative effectiveness analysis used meta-regression adjusted for methodological characteristics: held all effect sizes at the modal follow-up time (12.9 weeks), and mean attrition rate, substance use outcome type (alcohol, marijuana, other drugs), pretest differences, and overall group equivalence on

			treatment, group/mixed counseling, Psychoeducational therapy, pharmacological, self-help], with only modest differences from the other treatment types in this category. Overall, the mean effect sizes relative to TAU are in the 0.15–0.25 range. Using Cohen's U3 index, these effects translate into a 5% to 10% improvement relative to participants in the comparison conditions. Using the results from the comparison conditions in studies reporting the number of days youth consumed marijuana in the past month, an effect size of 0.25 translates into a reduction from an average of 9.7 days in the past month to 7.2 days in the past month—a 25% reduction." (p. 11)
			• CBT "showed positive effects relative to most of the comparisons in which they were involved" (p. 10)
			  ○ **CBT vs TAU**: 2 studies, adjusted M= -0.37 [-2.62, 1.89], unadjusted M= -0.83 [-3.13, 1.48]
			  ○ **ACC vs TAU**: 2 studies, adjusted M= -0.24 [-0.42, -0.05], unadjusted M= -0.30 [-0.74, 0.14]
			• "MET/CBT: These treatments are more effective than no-treatment control or practice as usual conditions but have minimal or small effects relative to other active treatment conditions. MET/CBT compares favorably with practice as usual conditions but unfavorably with [Assertive continuing care (ACC), behavioral therapy, CBT, MET, family therapy]." (p.10)
			  ○ **MET/CBT vs TAU**: 2 studies, adjusted M= -0.15 [-3.03, 2.73], unadjusted M= -0.35 [-1.93, 1.23]
			• "Group/mixed counseling, Psychoeducational therapy, pharmacological, self-help conditions: The outcomes of these treatments compare unfavorably with almost every treatment with which they are compared. They may be more effective than no-treatment control conditions, but the evidence for that is rather limited." (p. 10)
				risk, race, and sex. Positive mean effect sizes indicate that the intervention had, on average, better outcomes than the aggregate of all the treatment conditions with which they were compared,; negative indicates the treatment had worse outcomes. 95% confidence intervals are wide because of the small number of unique treatment–comparison combinations available for most comparisons.

Unknown Importance				

Level of Support	N/A	Systematic review: Hogue 2018[4]	**<u>Well-established</u>** outpatient behavioral treatments for adolescent SUD
			• **CBT** – Individual and group
			  ○ Hogue 2014 systematic review
			  ○ Burrow-Sánchez et al. (2015) SUD: culturally tailored CBT-G equivalent to standard CBT-G
			• **Adolescent CRA + ACC**
			  ○ Henderson et al. (2016) SUD 88%: Superior to TAU
			• **CBT/MET**
			  ○ Hogue 2014 systematic review
			  ○ Kelly et al. (2017) SUD: Equivalent to DC/12 but no substance use effects
			• **MET/CBT + FBT-B** (Behavioral Family-based Treatment)
				Adolescent SUD, Not stimulant specific
				
				Level of Support based on Journal of Clinical Child and Adolescent Psychology (JCCAP) criteria
				
				ACC = Assertive Continuing Care
				AOD = Alcohol and other drug

			○ Hogue 2014 systematic review ○ Stanger et al. (2015) cannabis use disorder: Equivalent to MET/CBT. **Probably efficacious** outpatient behavioral treatments for adolescent SUD • **MI/MET** ○ Hogue 2014 systematic review ○ de Gee et al. (2014) cannabis use: MI equivalent to information only ○ Walker et al. (2016) cannabis use: MET boosters superior to MET only ○ Winters et al. (2014) AUD or cannabis use disorder: MI + Parent session superior to assessment only; Equivalent to MI only **Possibly efficacious** outpatient behavioral treatments for adolescent SUD • **DC/12** (Drug counseling/12-step approach) ○ Hogue 2014 systematic review ○ Kelly et al. (2017) SUD: Equivalent to MET/CBT but no SU effects	FBT-E = Ecological Family-based treatment FBT-B = Behavioral Family-based Treatment BSFT = Brief strategic family therapy () DC/12 = Drug counseling/12-step approach

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include 291andomized or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Boger 2014[5]	***24*** wks Inpatient	CBT, DBT, MI, 12-step	N=40 (60% male; M age = 17.07, SD = 0.98)	"Reduction in depressive (t (1, 39)¼4.17, po.001) and anhedonic symptoms (t (1, 39)¼2.98, po.001); Increase in recognition of substance use problem (t (1, 39)¼3.15, po.001) and motivation to change substance use (t (1, 39)¼4.97, po.001); Improved reward responsiveness (F (1, 38)¼5.25, p¼.03) as a function of treatment."	In Babowitch & Anstehl 2016[6] SUD & depression systematic review
Huang 2011[7]	RCT Duration: Country: Taiwan Setting:	MET	N= 94 46 intervention 48 educational materials only	"By using the pretreatment scores as covariates, the intervention group demonstrated higher posttreatment scores of readiness to change and of the contemplation subscale on the University of Rhode Island Change Assessment than the control group. The results of this study support the finding that brief modified MET is effective in promoting	In German MA guideline (Braunwarth 2016, p. 203)[8]

				readiness to change MAMP and MDMA use behaviors in adolescents who receive short-term treatment programs."	
Hides 2011[9]	12 wks	CBT and MI	N=106 (63% male; M age=19.2, SD=1.6)	"Reductions in CES-D scores from baseline (M=29.1, SD=1.6) to post-treatment (M=18.9, SD=1.8) significant at po.05, however no change in HAM-D scores; Reduction in daily marijuana use quantity from baseline (M=1.2, SD=.2) to post-treatment (M=0.6, SD=1.2), and increased motivation for change from baseline (M=3.4, SD=.4) to post-treatment (M=1.0, SD=.5) significant at p<0.05; No change in alcohol or marijuana use days, number of alcoholic drinks per day or AUDIT scores." (Babowitch & Antshel 2016, p 28)[6]	In Babowitch & Anstehl 2016[6] SUD & depression systematic review
Hides 2010[10]	20 wks	CBT	N=60 (57% male; M age = 20.7, SD = 2.7)	"Reduction in DSM-IV MDD diagnoses from baseline (100.0%) to post-treatment (17.3%); Reduction in HAM-D scores from baseline (M=18.9, SD=0.6) to post-treatment (M=10.5, SD=0.7); Reduction in MASQ scores from baseline (M=41.2, SD=1.5) to post-treatment (M=28.0, SD=1.7) all significant at p<0.001; No change in DSM-IV criteria for SUD, drug and alcohol use days or abstinent days." (Babowitch & Antshel 2016, p 28)[6]	In Babowitch & Anstehl 2016[6] SUD & depression systematic review

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Therapy modalities including cognitive behavioral therapy, motivational enhancement therapy, motivational interviewing, and can be effective in decreasing substance use within adolescents. Utilizing individual and group-based settings and combining different modalities can increase the effectiveness of the therapies. Data specifically looking at the effect of other therapy modalities on stimulant use in adolescents is lacking, thus recommendations are based on how these therapies were utilized for other substance use disorders.		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Therapy may uncover other co-occurring disorders that may need treatment and could cause distress.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence from the research, but clinical encounters suggest that linking youth to various therapy modalities favors the outcome of decreased substance use and negative consequences of substance use.		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
The current research has small sample sizes, but does show that some therapy modalities (including CBT) have shown a reduction in substance use. However, there is no evidence looking directly at stimulant use disorder.	Clinicians should be aware that there has not been any evidence of adverse outcomes from engaging youth in therapy for stimulant use disorder.	☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
There was no evidence of values and preferences in the research about values and preferences of outcomes, but clinical encounters suggest that youth value outcomes including abstinence or harm reduction efforts.		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
There were no direct findings from the research about increasing equity through offering appropriate therapies, but clinical encounters suggest that providing options for therapeutic interventions would decrease inequities.	Risk of inequitable implementation exacerbating existing inequity.	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Certain therapeutic interventions including CBT have been shown to have a benefit for certain substances for youth who were willing to participate in the therapy and should be recommended.		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
Providing options for different therapy modalities for youth and their families is a feasible options clinicians should consider. Family therapy is a currently used treatment modality for adolescents with SUD.	There may be challenges in finding a therapist that takes the patients' insurance.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Data specifically looking at the effect of other therapy modalities on stimulant use in adolescents is lacking, thus CGC recommendations are based on how these therapies were utilized for other substance use disorders. Overall, CGC understands that there is no direct evidence from the research, but clinical encounters suggest that linking youth to various therapy modalities favors the outcome of decreased substance use and negative consequences of substance use. It is important to know there are various therapy modalities that can be offered with the understanding that some adolescents may find one or a combination of therapies most beneficial for stimulant use disorder.

Subgroup Considerations

None noted

Implementation Considerations

- Modality choice generally a matter of availability and joint patient/provider decision making

References

2. Dalton K, Bishop L, Darcy S. Investigating interventions that lead to the highest treatment retention for emerging adults with substance use disorder: A systematic review. *Addict Behav*. 2021;122:107005. Doi:10.1016/j.addbeh.2021.107005
3. Steele DW, Becker SJ, Danko KJ, et al. *Interventions for Substance Use Disorders in Adolescents: A Systematic Review*. Agency for Healthcare Research and Quality (US); 2020. Accessed May 23, 2022. http://www.ncbi.nlm.nih.gov/books/NBK557291/
4. Tanner-Smith EE, Steinka-Fry KT, Kettrey HH, Lipsey MW. *Adolescent Substance Use Treatment Effectiveness: A Systematic Review and Meta-Analysis*. Peabody Research Institute, Vanderbilt University; 2016:76.
5. Hogue A, Henderson CE, Becker SJ, Knight DK. Evidence Base on Outpatient Behavioral Treatments for Adolescent Substance Use, 2014-2017: Outcomes, Treatment Delivery, and Promising Horizons. *J Clin Child Adolesc Psychol*. 2018;47(4):499-526. Doi:10.1080/15374416.2018.1466307
6. Boger KD, Auerbach RP, Pechtel P, Busch AB, Greenfield SF, Pizzagalli DA. Co-occurring depressive and substance use disorders in adolescents: An examination of reward responsiveness during treatment. *J Psychother Integr*. 2014;24(2):109-121. Doi:10.1037/a0036975

7. Babowitch JD, Antshel KM. Adolescent treatment outcomes for comorbid depression and substance misuse: A systematic review and synthesis of the literature. *J Affect Disord*. 2016;201:25-33. Doi:10.1016/j.jad.2016.04.018
8. Huang YS, Tang TC, Lin CH, Yen CF. Effects of Motivational Enhancement Therapy on Readiness to Change MDMA and Methamphetamine Use Behaviors in Taiwanese Adolescents. *Substance Use Misuse*. 2011;46(4):411-416. Doi:10.3109/10826084.2010.501664
9. Braunwarth W, Christ M, Dirks H, Dyba J, Härtel-Petri R, Harfst T. *S3 Practice Guideline Methamphetamine-Related Disorders*. German Agency for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin; ÄZQ); 2016. Accessed November 18, 2022. https://www.aezq.de/mdb/edocs/pdf/literatur/s3-gl-methamphetamine-related-disorders-long.pdf
10. Hides LM, Elkins KS, Scaffidi A, Cotton SM, Carroll S, Lubman DI. Does the addition of integrated cognitive behaviour therapy and motivational interviewing improve the outcomes of standard care for young people with comorbid depression and substance misuse? *Med J Aust*. 2011;195(S3). Doi:10.5694/j.1326-5377.2011.tb03263.x
11. Hides L, Carroll S, Catania L, et al. Outcomes of an integrated cognitive behaviour therapy (CBT) treatment program for co-occurring depression and substance misuse in young people. *J Affect Disord*. 2010;121(1-2):169-174. doi:10.1016/j.jad.2009.06.002

Table 24. Family Therapy

Recommendation: When treating adolescents and young adults for StUD, clinicians should consider delivering behavioral interventions that have been demonstrated to be effective in the treatment of other SUDs in adolescents (eg, CM, CBT, CRA, **Family Therapy**) and in the treatment of StUDs in adults (eg, CM, CBT, CRA).

Clinical Question Summary

Clinical Question	1. Is family therapy effective in treating adolescents and young adults with stimulant use disorder? 2. What contextual factors and implementation strategies may influence the effects of family therapy?
Population	Adolescent and young adult patients with stimulant use disorder
Intervention	Any form of Family Therapy
Comparison	TAU
Main Outcomes	Stimulant use, substance use, treatment retention, treatment attendance
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Notes • Types of providers that provide family therapy, CBT, or other modalities, such as whether the provider was a licensed clinical social worker, licensed professional counselor, licensed clinical psychologist, psychiatrist, or other staff.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized control trial, **StUD**: Stimulant use disorder, **SUD**: Substance use disorder, **TAU**: Treatment as usual, **UDS**: Urine drug screen, **UDT**: Urine drug test
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Substance use	N/A	Meta-analysis: Tanner-Smith 2016[1] (Not rated)	Pre-Post change in substance use after intake effect size [95% CI]: • "The largest reductions were observed for MET/CBT, family therapy, and CBT programs." (p. 1) ○ **Family Therapy**: 13 studies, Hedges g=1.11 [0.89, 1.33]	Adolescent SUD, Not stimulant specific.

			○ **TAU**: 11 studies, Hedges g=0.86 [0.61, 1.11] ○ **No treatment**: 8 studies, Hedges g=0.96 [0.74, 1.18] Mean Group Posttest Comparison Effect Size [95% CI]: • "Overall, the mean effect sizes relative to TAU are in the 0.15–0.25 range. Using Cohen's U3 index, these effects translate into a 5% to 10% improvement relative to participants in the comparison conditions. Using the results from the comparison conditions in studies reporting the number of days youth consumed marijuana in the past month, an effect size of 0.25 translates into a reduction from an average of 9.7 days in the past month to 7.2 days in the past month—a 25% reduction. " (p 11) • "Family therapy… showed a positive mean effect size across all the comparisons in which it was involved." (p. 10) ○ **Family Therapy vs TAU**: 5 studies, adjusted M=0.14 [-0.16, 0.44], unadjusted M= -0.21 [-0.52, 0.10] ○ **Family Therapy vs Any Comparator**: 18 studies adjusted M=0.08 [-0.07, 0.24], unadjusted M=0.18 [0.01, 0.35] ○ **Family Therapy vs CBT**: 3 studies, M=0.14 [-1.11, 1.39] ○ **Family Therapy vs MET/CBT**: 3 studies, M=0.05 [-0.54, 0.63]	Note, results of the 2 analyses not fully comparable, mostly from missing baselines in Pre-Post analysis. Comparative effectiveness analysis used meta-regression adjusted for methodological characteristics: modal follow-up time (12.9 weeks), mean attrition rate, substance use outcome type (alcohol, marijuana, other drugs), pretest differences, and overall group equivalence on risk, race, and sex. Positive indicates the intervention had, on average, better outcomes than the aggregate of all the treatment conditions with which they were compared,; negative indicates worse outcomes. 95% confidence intervals are wide because of the small number of unique treatment–comparison combinations available for most comparisons.
Alcohol use	N/A	Meta-analysis: Steele 2020[2] (Not rated)	**Family Therapy vs TAU**: "Across multiple intensive interventions, Fam was most effective, reducing alcohol use days by 3.5 days/month compared with treatment as usual." (p. vii) Strength of evidence: Low. "Participants who received Fam versus TAU had an NMD [net mean difference] of −3.5 (95% CrI −6.9, -0.4) days of alcohol use per month. We rated the associated SoE for this effect as low." (Steele et al., 2020, p. 55) in the network meta-analysis	Adolescent SUD, Not stimulant specific
Unknown Importance				
Level of Support (based on Journal of Clinical Child	N/A	Meta-analysis: Hartnett 2017[3] (Not rated)	Functional Family Therapy vs Untreated Controls • Random assignment studies: k=3, n=165, d=0.48, p<0.01 • Nonrandom assignment studies: k=2, n=548, d=0.90, nsd	nsd = no significant difference

and Adolescent Psychology criteria)			Functional Family Therapy vs TAU • Random assignment studies: k =3, n=250, d=0.20, nsd • Nonrandom assignment studies: k=2, n=130, d=0.08, nsd Functional Family Therapy vs Alternative Treatments • Random assignment studies: k =5, n=406, d=0.35, p<0.05 • Nonrandom assignment studies: k=3, n=175, d=0.75, p<0.001	
		Systematic review: Hogue 2018[4] (Not rated)	**Well-established** outpatient behavioral treatments for adolescent SUD • FBT-E (Ecological Family-based treatment) o Hogue 2014 systematic review • MDFT (Multidimensional family therapy) o Dakof et al. (2015) SUD: Equivalent to group CBT • FFT (Functional Family Therapy) o Rohde et al. (2014) SUD & Depression: Delivering FFT and a depression protocol sequentially is superior to delivering them simultaneously • MET/CBT + FBT-B (Behavioral Family-based Treatment) o Hogue 2014 systematic review; Stanger et al. (2015) cannabis use disorder: Equivalent to MET/CBT **Probably efficacious** outpatient behavioral treatments for adolescent SUD • FBT-B (Behavioral Family-based Treatment) o Hogue 2014 systematic review • BSFT (Brief strategic family therapy) o Horigian et al. (2015) SUD 73%: Equivalent to TAU • CM + FBT-B o Hogue 2014 systematic review; Letourneau et al. (2017) AOD use: Equivalent to TAU. • CM + MET/CBT + FBT-B o Stanger et al. (2015) cannabis use disorder: Superior to MET/CBT during CM period, but NSD at 1-year follow-up. NSD from MET/CBT + CM (Family had no additional effect). CM was 3 months of continuing care following treatment; Hogue 2014 systematic review	Adolescent SUD, Not stimulant specific Level of Support AOD = Alcohol and other drug FBT-E = Ecological Family-based treatment FBT-B = Behavioral Family-based Treatment BSFT = Brief strategic family therapy () DC/12 = Drug counseling/12-step approach

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design, Participants	Interventions	Outcomes	Comments
Henggeler 2006[5]	RCT Duration: 4 mo Country: USA Setting: Outpatient N=161 juvenile-justice involved adolescents with alcohol, cannabis, **cocaine** use disorder	**Drug court+Group counseling**: Drug court with usual community services (including peer group therapy) **Family court+Group counseling**: Family court with usual community services (including peer group therapy), **Drug court+Group counseling+Family therapy:** Drug court combined with family therapy using an ecological model and peer group therapy, **Drug court+Group counseling+Family therapy+CM**: Drug court combined with family therapy using an ecological model and peer group therapy and contingency management		
Joanning 1992[6]	RCT USA Outpatient N=134 adolescents with problematic use of alcohol, cannabis, **amphetamines**, barbiturates, or hallucinogens	**Group counseling:** Adolescent group therapy **Family therapy:** Family systems therapy using a structural model **Family education:** Family therapy (group) using an educational mode "Family drug education"		In Tanner-Smith 2016[1]
Letourneau 2017[7]	RCT USA Outpatient N=107 juvenile-justice involved adolescents. Baseline use: **1% stimulants**, 40% alcohol, 87% cannabis, 23% opioids.	**CBT+Family therapy+CM:** Risk reduction therapy for adolescents + behavioral family therapy + CM **TAU (group):** "Usual services"		In Hogue 2018[4]
Liddle 2018[8]	RCT USA Outpatient N=113 adolescents with cannabis, alcohol, **stimulant**, opioid use disorder	**Family therapy:** Multidimensional family therapy, a form of ecological family therapy **TAU (group):** Residential treatment		Not in tanner, a bunch of other Liddle papers are.

Rohde 2014[9]	RCT Duration: 20 wks with 12 mo follow-up Setting: Outpatient Country: USA N=170 adolescents with a current DSM-IV depression disorder and non-nicotine **substance** use disorder; drug use within the last 90 days (TLFB)	**Simultaneous FFT & CWD**: Functional Family Therapy (FFT) is a behaviorally-based model of family therapy (Alexander 1982) that targets addictive behaviors. A points system was added to reward participation. Adolescent Coping With Depression course (CWD) provides cognitive and behavioral strategies to address adolescent depression (Clarke 1990)., **Family therapy + CWD:** FFT followed by adolescent CWD **CWD + Family therapy:** Adolescent CWD followed by FFT		In Tanner-Smith 2016[1] and Hogue 2018[4]
Santisteban 2011[10]				In Tanner-Smith 2016[1]
Slesnick 2005[11]				In Tanner-Smith 2016[1]

Existing Guidelines

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Other Resources

Source	**Resource**	**Comments**
SAMHSA	Substance Abuse and Mental Health Services Administration. (2020k). Substance use disorder treatment and family therapy. Treatment Improvement Protocol (TIP) Series 39. SAMHSA Publication No. PEP20-0202-012. Substance Abuse and Mental Health Services Administration.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Existing data suggests that utilizing family therapy can be more effective than other therapy modalities in reducing substance use in youth with substance use disorders, but this research is not specific for stimulant use disorders.	Ensure that family members are willing to engage in ongoing therapy where they will have to both attend and participate.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
None identified.	Family therapy may uncover other co-occurring disorders in family members that may need treatment. The appropriateness of family therapy should be carefully considered in families in which a young person may have experienced abuse or neglect, or in which a parent is actively using substances.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Given supportive data for family therapy for substance use interventions in youth and no recorded evidence of undesirable effects, the limited evidence favors the intervention.	The data for stimulant use disorder will be generalized from how family therapy has been successful in treatment for other substance use disorders.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
2 meta-analyses suggest that family therapy is more effective for substance use disorder and alcohol use disorder, in particular, compared to other modalities, but there are no studies specifically looking at the role family therapy plays in stimulant use disorder treatment for youth.		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low: ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
There was no evidence regarding values and preferences in the research about values and preferences of outcomes, but clinical encounters suggest that youth value outcomes including abstinence or harm reduction efforts.		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Providing access to family therapy can decrease the inequities in stimulant use disorder treatment. Risk of inequitable implementation exacerbating existing inequity.	☐ Increased ☐ Probably increased ☒ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Family therapy has been shown to be effective for substance use disorders in youth and would be an acceptable clinical intervention.		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence does not discuss the feasibility of accessing family therapists who are willing to treat youth with stimulant use disorder. Family therapy is a currently used treatment modality for adolescents with SUD.	In clinical practice, it can be challenging to find a family therapist that takes insurance and is comfortable managing stimulant use disorder in youth.	☐ No ☐ Probably no ☒ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Current data suggests that utilizing family therapy can be more effective than other therapy modalities in reducing substance use in youth with substance use disorders and alcohol use disorder, but this research is not specific for stimulant use disorders. However, given the success in reducing other substances use, the CGC infers that family therapy could also be effective and appropriate to recommend for adolescents with stimulant use disorder who consent to family therapy. It is important to recognize that family therapy may uncover other dynamics including co-occurring disorders in other family members or challenges in communication between family members that may impact the adolescents' engagement in continuing family therapy.

Subgroup Considerations

- Adolescents in state custody or with DCFS involvement because of abuse, neglect, parental substance use, or other concern with family members
    - Family therapy would need to be undertaken cautiously and thoughtfully

Implementation Considerations

- Families may have to meet more than 1 family therapist to determine if they are a right fit for the family and their treatment goals
- Family therapy is often helpful in establishing goals and communication strategies around substance use, but we can also begin to understand how the dynamic of the family may/may contribute to ongoing substance use (including setting up structure/boundaries/consequences at home).
- Think broadly on how we define "family"

References

1. Tanner-Smith EE, Steinka-Fry KT, Kettrey HH, Lipsey MW. *Adolescent Substance Use Treatment Effectiveness: A Systematic Review and Meta-Analysis*. Peabody Research Institute, Vanderbilt University; 2016:76.
2. Steele DW, Becker SJ, Danko KJ, et al. *Interventions for Substance Use Disorders in Adolescents: A Systematic Review*. Agency for Healthcare Research and Quality (US); 2020. Accessed May 23, 2022. http://www.ncbi.nlm.nih.gov/books/NBK557291/
3. Hartnett D, Carr A, Hamilton E, O'Reilly G. The Effectiveness of Functional Family Therapy for Adolescent Behavioral and Substance Misuse Problems: A Meta-Analysis. *Fam Process*. 2017;56(3):607-619. doi:10.1111/famp.12256
4. Hogue A, Henderson CE, Becker SJ, Knight DK. Evidence Base on Outpatient Behavioral Treatments for Adolescent Substance Use, 2014-2017: Outcomes, Treatment Delivery, and Promising Horizons. *J Clin Child Adolesc Psychol*. 2018;47(4):499-526. doi:10.1080/15374416.2018.1466307
5. Henggeler SW, Halliday-Boykins CA, Cunningham PB, Randall J, Shapiro SB, Chapman JE. Juvenile drug court: Enhancing outcomes by integrating evidence-based treatments. *J Consult Clin Psychol*. 2006;74(1):42-54. doi:10.1037/0022-006X.74.1.42

6. Joanning H, Quinn W, Thomas F, Mullen R. Treating adolescent drug abuse: a comparison of family systems therapy, group therapy, and family drug education. *J Marital Fam Ther*. 1992;18(4):345-356. doi:10.1111/j.1752-0606.1992.tb00948.x
7. Letourneau EJ, McCart MR, Sheidow AJ, Mauro PM. First Evaluation of a Contingency Management Intervention Addressing Adolescent Substance Use and Sexual Risk Behaviors: Risk Reduction Therapy for Adolescents. *J Subst Use Addict Treat*. 2017;72:56-65. doi:10.1016/j.jsat.2016.08.019
8. Liddle HA, Dakof GA, Rowe CL, et al. Multidimensional Family Therapy as a community-based alternative to residential treatment for adolescents with substance use and co-occurring mental health disorders. *J Subst Use Addict Treat*. 2018;90:47-56. doi:10.1016/j.jsat.2018.04.011
9. Rohde P, Waldron HB, Turner CW, Brody J, Jorgensen J. Sequenced Versus Coordinated Treatment for Adolescents with Comorbid Depressive and Substance Use Disorders. *J Consult Clin Psychol*. 2014;82(2):342. doi:10.1037/a0035808
10. Santisteban DA, Mena MP, McCabe BE. Preliminary results for an adaptive family treatment for drug abuse in Hispanic youth. *J Fam Psychol*. 2011;25(4):610-614. doi:10.1037/a0024016
11. Slesnick N, Prestopnik JL. Ecologically based family therapy outcome with substance abusing runaway adolescents. *J Adolesc*. 2005;28(2):277-298. doi:10.1016/j.adolescence.2005.02.008

Table 25. Specific Treatment

Recommendation: When treating adolescents and young adults for StUD, clinicians should use an adolescent-specific treatment model (eg, A-CRA) or tailor existing treatments to be developmentally responsive.

Clinical Question Summary

Clinical Question	1. Are adolescent-specific behavioral treatment models (eg, A-CRA) effective and appropriate treatment for StUD in adolescents and young adults? 2. Should adolescents be referred to adolescent-specific behavioral treatment models (eg, A-CRA) or are adult treatment models effective and appropriate? 3. What modifications should be made so that behavioral treatment is delivered in a developmentally appropriate manner?
Population	Adolescent (age 12-17) and young adult (age 18-25) patients with stimulant use disorder
Intervention	Adolescent-specific behavioral treatment model for StUD or SUD (eg, Adolescent CRA)
Comparison	Adult or general treatment models used for treating StUD (eg, CM, CBT, CRA)
Main Outcomes	Stimulant use, substance use, treatment retention, treatment attendance
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Adolescent Community Reinforcement Approach is a CBT model tailored to adolescents
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATSUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **YA**: Young adult
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No research evidence was found in the literature review of **adolescent/YA-specific behavioral treatment for StUD** or head-to-head **comparison of adolescent/YA-specific to adult treatment for StUD**.

Not stimulant-specific: "Two studies examined CBT, one a CBT-I [Individual] approach and the other CBT-G [Group], both of which were designated Well-Established in the 2014 EBU. Henderson and colleagues (2016) completed an independent replication of **Adolescent Community Reinforcement Approach (A-CRA),** a CBT-I model that was tested against usual care provided to youth under community supervision by juvenile probation. Youth randomized to A-CRA also received 3 months of assertive continuing care (Godley, Godley, Dennis, Funk, & Passetti, 2002) following treatment. A-CRA was superior to usual care in decreasing SU-related problems and had moderate effects for frequency of alcohol and other drug (AOD) use at 1-year follow-up (FU). This replication study newly qualifies A-CRA as a Well-Established treatment model, a notable achievement previously reached by two FBT-E models (MDFT, FFT)." (Hogue 2018, p. 8)[1]

Existing Guidelines

SAMHSA. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration; 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Manning V, Arunogiri S, Frei M, et al. *Alcohol and Other Drug Withdrawal: Practice Guidelines*. 3rd ed. Turning Point; 2018.

Levy SJL, Williams JF, Committee on Substance Use and Prevention. Substance Use Screening, Brief Intervention, and Referral to Treatment. *Pediatrics*. 2016;138(1):e20161211. doi:10.1542/peds.2016-1211

NSW Ministry of Health. *Drug and Alcohol Withdrawal Clinical Practice Guidelines (Reviewed 2018)*. NSW Health; 2008. Accessed September 16, 2021. www.health.nsw.gov.au

Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Ryan 2019[2]	• "With low levels of use, the provider may elect to do brief intervention in the office setting, using Screening, Brief Intervention, and Referral Treatment approaches.38" (Ryan, 2019, p. 1142) • "it is reasonable to start with individual or group outpatient sessions, when it has been determined that the youth has either cocaine use or mild cocaine use disorder." (Ryan, 2019, p. 1142) • "If the youth cannot adhere to treatment recommendations, or when there is a moderate cocaine use disorder, referral to an intensive outpatient program, augmented by either family-based therapy or contingency management components may be necessary." (Ryan, 2019, p. 1142) • "If there is continued inability to comply with recommendations, significant relapse, or a severe cocaine use disorder, residential treatment may be necessary." (Ryan, 2019, p. 1143)	

Other Resources

Source	Resource	Comments
American Academy of Pediatrics	Substance Use Screening, Brief Intervention, and Referral to Treatment (https:// pediatrics.aappublications.org/content/138/1/ e20161211)	
SAMHSA 2012	TIP 31: Screening and Assessing Adolescents for Substance Use Disorders (https://store. samhsa.gov/product/SMA12-4079): TIP 31 describes strategies, procedures, and screening and assessment instruments that are appropriate for the initial detection of substance use among adolescents, the comprehensive assessment of their problems, and subsequent treatment planning. It summarizes each instrument in the appendixes.	
	Finding Quality Treatment for Substance Use Disorders (https://store.samhsa.gov/product/ PEP18-TREATMENT-LOC): This resource is for people seeking behavioral health services and treatment for SUDs. It provides guidance on how to find a quality treatment center and the steps to complete before accessing treatment.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
There is no specific evidence around stimulant use disorder in youth and these findings were taken from broader recommendations for substance use disorders in youth.	Adolescent-specific models or tailored treatment for SUD are expected to be effective, and are expected to be moderately more effective than non-specific treatment. The standard of care is to use adolescent-specific treatment for SUDs. This standard should be extended to StUD.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	There is a risk of exposing youth to peers or young adults who are using other substances when referring to other levels of care, which may increase the likelihood of a youth using another substance.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Ensuring youth have access to an appropriate level of care that is tailored to their needs would be more effective in treating their stimulant use disorder than the possibility of exposing them to peers who use other substances.	Clinicians should ensure that referrals take into account age of population served by the level of care, accessibility (public transport, allow drop-ins), provide assertive follow-up and reminders, and those that focus on developing strategies for dealing with peer-related motivators for use.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Given limited evidence, these recommendations are based on clinicians with subject matter expertise in treating youth with substance use disorder.		☒ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☐ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
There was no evidence of values and preferences in the literature review about values and preferences of outcomes, but clinical encounters suggest that youth value outcomes including abstinence or harm reduction efforts.		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
There were no direct findings from the literature review about increasing equity through offering appropriate referrals, but clinical encounters suggest that providing appropriate referrals would decrease inequities.	Clinicians should be aware that youth with increased ACE (adverse childhood events) have an increased risk of SUD and providing appropriate referrals may decrease health inequities that these populations face.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
There were no direct findings from the literature review about the acceptability of different levels of care to patients/non patients.	Clinicians should take into consideration that some families may feel stigmatized (cultural/religious, etc) by referral to some levels of care.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
There were no direct findings from the literature review about feasibility for patients/caregivers.	There are very few adolescent-specific SUD treatment models.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

The CGC recognizes that there are no data on adolescents' receipt of adolescent-specific or developmentally responsive treatment for stimulant use disorder. The standard of care for SUDs is to use adolescent-specific treatment and the CGC's view is that this standard should be extended to StUD. Adolescent-specific models or tailored treatment for SUD are expected to be effective, and are expected to be moderately more effective than non-specific treatment. Ensuring youth have access to an appropriate level of care that is tailored to their needs would be more effective in treating their stimulant use disorder than the possibility of exposing them to peers who use other substances. Given limited evidence, these recommendations are based on clinicians with subject matter expertise in treating youth with substance use disorder.

Subgroup Considerations

None noted

Implementation Considerations

- Adolescent patients should be referred to the most appropriate level of care while maintaining the least restrictive environment. Tailor a referral that is adolescent-specific, accessible, and encourages ongoing contact and support. Peer-based services may provide youth with an additional level of support.
- Be explicit regarding confidentiality. Reinforce confidentiality throughout treatment if patients are hesitant to disclose.

References

1. Hogue A, Henderson CE, Becker SJ, Knight DK. Evidence Base on Outpatient Behavioral Treatments for Adolescent Substance Use, 2014-2017: Outcomes, Treatment Delivery, and Promising Horizons. *J Clin Child Adolesc Psychol*. 2018;47(4):499-526. doi:10.1080/15374416.2018.1466307
2. Ryan SA. Cocaine Use in Adolescents and Young Adults. *Pediatr Clin North Am*. 2019;66(6):1135-1147. doi:10.1016/j.pcl.2019.08.014

Table 26. Group Treatment

Recommendation: When treating adolescents and young adults for StUD, clinicians should use peer-age groups for behavioral treatment in group formats when possible and avoid incorporating adolescents and young adults into group behavioral treatment with older adults.

Clinical Question Summary

Clinical Question	1. Are there modifications that should be made to behavioral treatment so that it is delivered in a developmentally appropriate manner to adolescent and young adult patients? 2. Should adolescents and young adult who use stimulants be referred to adolescent/YA-specific group-based treatment or is adult group-based treatment as effective and appropriate?
Population	Adolescent (age 12-17) and young adult (age 18-25) patients with stimulant use disorder
Intervention	Group counseling or therapy for StUD
Comparison	TAU
Main Outcomes	Stimulant use, substance use, treatment retention, treatment attendance
Setting	Inpatient or outpatient specialty SUD treatment
Background & Definitions	Survey evidence suggests that adolescents and young adults prefer to be in groups comprised of peers their own age
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Existing Guidelines

Manning V, Arunogiri S, Frei M, et al. *Alcohol and Other Drug Withdrawal: Practice Guidelines*. 3rd ed. Turning Point; 2018.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ None ☐ Small ☐ Moderate ☐ Large

		☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Clinical experience and best practices approach suggests that there could be a negative influence from combining age groups. Being exposed to older individuals that tend to have used substances for longer and therefore tend to have developed more severe substance use disorders can reduce the effectiveness of behavioral interventions for adolescents and young adults and increase their experience of negative peer pressure.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Survey evidence that adolescents and young adults prefer to be in groups comprised of their own age group (Bagley et al., 2023).	☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Survey evidence that adolescents and young adults prefer to be in groups comprised of their own age group (Bagley et al., 2023).	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Clinical experience and best practice approaches suggest a potential negative influence from combining age groups.

Subgroup Considerations

None noted

Implementation Considerations

Group counseling and therapy requires clinical skills

Table 27. Pharmacotherapy

Recommendation: When treating adolescents and young adults for StUD, clinicians should consider treating youth with StUD with the off-label pharmacotherapies detailed in the Pharmacotherapy section when the developmentally contextualized benefits outweigh the harms.

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate pharmacotherapies for the treatment of stimulant use disorder in adolescent and young adult patients? 2. What contextual factors and implementation strategies may influence the effects of pharmacotherapy?
Population	Adolescent and young adult patients with stimulant use disorder
Intervention	Any pharmacotherapy for stimulant use disorder
Comparison	TAU
Main Outcomes	Stimulant use, substance use, treatment completion, treatment retention
Setting	Outpatient
Background & Definitions	Available clinical trials did not include adolescents, but are likely to apply
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized control trial, **StUD**: Stimulant use disorder, **SUD**: Substance use disorder, **TAU**: Treatment as usual, **UDS**: Urine drug screen, **UDT**: Urine drug test
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Efficacy	N/A	Meta-analysis: Zhou 2015[1] (Not assessed)	Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders. "Two of the trials meeting inclusion criteria recruited only patients with alcohol use [38,40]; three recruited patients with alcohol and cannabis use [39,41,42]" (Zhou et al., 2015, p. 40)	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Limitations
Boger 2014[2]					Babowitch & Antshel 2016[3]
Cornelius 2010[4]	RCT Duration: Country: Setting:	Fluoxetine	N= comorbid MDD-CUD youth and young adults		
Heinzerling 2013[5]	RCT 8 wks USA Outpatient	**Bupropion** SR 150 mg twice daily **Placebo** All patients also received outpatient substance abuse counseling.	N=19 adolescents (age 14-21) with DSM-IV **methamphetamine** abuse (n = 2) or dependence (n = 17), low frequency of methamphetamine use (use on ≤ 18/30 days)	Treatment Effectiveness Score (TES, mean number of MA negative twice weekly UDS during treatment) significantly higher in the placebo group compared to bupropion group. No difference in treatment retention.	
Riggs 2007[6]	RCT 16 wks	Fluoxetine Placebo All patients also received CBT	N=126 (67% male; M age =17.2, SD=1.7)	CDRS-R Self-report Reduction in CDRS-R raw mean scores from baseline (M=50.75 [48.04–53.45]) to post-treatment (M=25.99 [23.10–28.88]) as a function of fluoxetine plus CBT; No change in number of substance use days as a function of treatment group.	Babowitch & Antshel 2016[3]

Existing Guidelines

McIver C, Flynn J, Baigent M, et al. *Management of Methamphetamine Psychosis, Stage 2: Acute Care Interventions for the Treatment of Methamphetamine Psychosis & Assertive Community Care for the Post-Discharge Treatment of Methamphetamine Psychosis*. Drug and Alcohol Services South Australia; 2006.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Based on expert opinion and examination of adult-focused studies. Clinical trials of pharmacotherapy for stimulant use disorder are largely focused on adults ≥18 and do not include adolescents <18. Such studies also typically include young adults ≥18 alongside older adults without separate analyses of the young adult population.	Although studies do not typically include adolescents <18, the CGC felt it is likely that many of the benefits observed in high-quality clinical trials of adults ≥18 would also be seen in older adolescents (eg, 16- and 17-year-olds).	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Based on expert opinion and examination of adult trials.	Notably, one medication for addiction treatment (ie, varenicline in the treatment of nicotine use disorder) is a medication with approval for individuals ≥17 in the US, but for adolescents <17, it is associated with harmful outcomes. Thus, the CGC acknowledges that there is potential harm in use of pharmacotherapy in adolescents despite a benefit in adults only a few years older.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Based on expert opinion and examination of adult trials.	Given that stimulant use disorder is, in some cases, a life-threatening condition (ie, secondary to overdose), there are likely situations in which, on a case-by-case basis, a clinician would expect that the benefits of treatment with pharmacotherapy would outweigh potential harms.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Data are stronger for adults ≥18 years; very few data exist for adolescents <18 years.	The recommendation to offer pharmacotherapy to adolescents is expert opinion; recommendation to offer pharmacotherapy to young adults is based on small amount of clinical trial data.	☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
Ideal outcomes for adolescents and young adults with stimulant use disorders have not been well characterized. To date, most studies rely on abstinence from substance use as the primary outcome.		☐ Yes ☒ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusions

Justification

Although the available clinical trials did not typically include adolescents <18, it is likely that many of the same benefits observed by adults ≥18 would be expected in older adolescents (eg, 16- and 17-year-olds). The CGC cannot routinely recommend use of pharmacotherapy in adolescents <18 given the lack of approval for this age group. Nonetheless, the CGC felt that given the potentially life-threatening consequences of stimulant use disorder, clinicians might consider pharmacotherapy on a case-by-case basis, balancing potential benefits and harms.

Subgroup Considerations

None noted

Implementation Considerations

Consideration of potential benefits vs harms important

References

1. Zhou X, Qin B, Del Giovane C, et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: a systematic review and meta-analysis. *Addict Abingdon Engl*. 2015;110(1):38-48. doi:10.1111/add.12698
2. Boger KD, Auerbach RP, Pechtel P, Busch AB, Greenfield SF, Pizzagalli DA. Co-occurring depressive and substance use disorders in adolescents: An examination of reward responsiveness during treatment. *J Psychother Integr*. 2014;24(2):109-121. doi:10.1037/a0036975
3. Babowitch JD, Antshel KM. Adolescent treatment outcomes for comorbid depression and substance misuse: A systematic review and synthesis of the literature. *J Affect Disord*. 2016;201:25-33. doi:10.1016/j.jad.2016.04.018
4. Cornelius JR, Bukstein OG, Douaihy AB, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend*. 2010;112(1-2):39-45. doi:10.1016/j.drugalcdep.2010.05.010
5. Heinzerling KG, Gadzhyan J, van Oudheusden H, Rodrigues F, McCracken J, Shoptaw S. Pilot randomized trial of bupropion for adolescent methamphetamine abuse/dependence. *J Adolesc Health Off Publ Soc Adolesc Med*. 2013;52(4):502-505. doi:10.1016/j.jadohealth.2012.10.275
6. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A Randomized Controlled Trial of Fluoxetine and Cognitive Behavioral Therapy in Adolescents With Major Depression, Behavior Problems, and Substance Use Disorders. *Arch Pediatr Adolesc Med*. 2007;161(11):1026. doi:10.1001/archpedi.161.11.1026

Pregnant and Postpartum Patients

Table 28. Prenatal Care Referral

Recommendation:

1. Clinicians should incorporate additional elements into the comprehensive assessment of StUD for patients who are pregnant, including:
    a. providing referrals to prenatal care providers if not already established.
2. Coordination of prenatal care and treatment of StUD is encouraged.

Clinical Question Summary Table

Clinical Question	1. What additional consideration should clinicians have when evaluating stimulant use disorder in persons who are pregnant? 2. What additional considerations should be included when establishing a treatment plan for stimulant use disorder in persons who are pregnant?
Population	Pregnant patients being assessed for stimulant use disorder
Intervention	Referral to prenatal care provider if the patient does not already have one, Referral to Maternal/Fetal Medicine specialist is necessary
Comparison	No referral
Main Outcomes	Prenatal care attendance, pregnancy outcomes
Setting	Outpatient prenatal care
Perspective	Individual level
Background & Definitions	Notes • "ATS use in pregnancy is associated with poor antenatal care and adverse, short-term social outcomes. Level of evidence: III-2" (NSWMH 2014, p 88)[1] • Coordinated SUD and prenatal care programs: "The programs identified offer support from the prenatal period through to postpartum, with some extending follow-up supports until the infant's first birthday or beyond. Many of the programs use an interdisciplinary team of providers to meet a range of needs for their clients including health, social and interpersonal needs that extend beyond conventional notions of perinatal health and substance use.23–25" (Ackerman 2021, p 224)[2].
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **n.s.d.:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Program characteristics	N/A	Systematic review: Ackerman 2021[2]	Recommendations for further support measures identified in the results: (p. 236) • Removal of punishment and stigmatization (n = 1) Dinger et al. (2017) • Family-oriented and gender-specific approach to harm reduction for addiction in pregnancy (n = 1) Smid (2017) • Greater parental monitoring and home life for children with prenatal MA exposure (n = 1) Smith et al. (2016) • Involvement with prenatal services such as monthly ultrasound can act as a strong motivator for addiction treatment (n = 1) Chatterjee (2018) • Multidisciplinary interventions/approaches for mothers that use MA during pregnancy (n = 1) Gutwinski et al. (2017) • Reinforcement-based therapy (n = 1) Forray et al. (2015)	Interventions for women with MA use in pregnancy

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Burkett 1998[3]	Prospective Jan 1-Dec 31, 1989 USA	**Comparator(s)** (1) Cocaine users receiving prenatal care and drug rehabilitation ("comprehensive care") (n=278) (2) Cocaine users receiving prenatal care only (n=206) (3) Cocaine users receiving minimal or no care (n=421)	N=1,055 pregnancies, 905 cocaine or crack users, 150 nonusers recruited from prenatal clinic or enrolled at labor and delivery.	**Maternal and fetal complications: Anemia**: Higher risk in minimal/no care cocaine users than nonusers (OR 28, 95% CI 4.2-103.2) **Weight under 100 lb**: Higher risk in minimal/no care cocaine users than nonusers (OR 28, 95% CI 4.2-103.2) **Urinary tract infections**: Higher risk in minimal/no care cocaine users than nonusers (OR 2.4, 95% CI 1.8-5.0) **Syphilis**: Higher risk in cocaine users (all groups) compared to nonusers (OR 15, 95% CI 4.6-36.1)	Prenatal care can protect against many of the maternal and fetal complications associated with cocaine use during pregnancy.

		(4) Non-cocaine users (n=150)		**Other STI**: Higher risk in cocaine users (all groups) compared to nonusers (OR 11.2, 95% CI 4.0-35.8) **Death**: 4 in minimal/no care cocaine users **Myocardial infarction**: 2 in minimal/no care cocaine users **Small for gestational age (SGA**): NSD between comprehensive care cocaine users and nonusers. Higher risk in minimal/no care + prenatal care cocaine users than comprehensive care users + nonusers **Stillbirth**: NSD between comprehensive care cocaine users and nonusers. Lower rate in comprehensive care users (8.3%) + nonusers (6%) than prenatal care only (13.1%). Higher rate in prenatal care only (13.1%) than minimal/no care (39.2%) **Term pregnancy**: NSD between comprehensive care cocaine users and nonusers. Higher rate in comprehensive care users (90.2%) + nonusers (94%) than prenatal care only (80.6%). Higher rate in prenatal care only (80.6%) than minimal/no care (49.4%) Mean gestational age: Birth weight: Drug screening Attendance: Pregnancy: One year following delivery HIV seroconversion: One year following delivery	
Carroll 1995[4]	RCT Duration: average 23 weeks (range 13 to 31 weeks) USA Outpatient	(1) **Intervention + TAU:** Weekly prenatal classes, weekly relapse-prevention groups, childcare during treatment visits, and CM (incentives for three consecutive negative urine screens).	N=20 pregnant women enrolled in methadone maintenance. 2.7 mean days cocaine use in past 30 days	**Attrition:** 4/20 (20%) dropout rate **Prenatal care visits**: Intervention group attended more prenatal visits on average than standard treatment (n=14, 15 vs 5 visits, $p<0.01$). **Cocaine use**: n.s.d. in % cocaine-positive UDTs (n=14). Same for opiates and other drugs. **Gestational age at delivery:** Longer median gestation time in intervention group than	In Terplan 2015[5] Risk of bias: High for attrition Also in Preg CM

		(2) **TAU**: All participants received methadone maintenance (MMT) of weekly group counselling and UDS 3x/wk.		standard treatment (n=14, 40 vs 38 weeks, p-val not reported). **Weight**: Heavier median birth weight in intervention group (n=14, 3.348 vs 2.951 grams, p-val not reported). **Days hospitalized**: n.s.d. in length of time infants remained in the hospital after delivery for detoxication (n=14, p-val not reported).	
Kropp 2010[6] secondary analysis of Winhusen 2008[7]	RCT Duration: 1 mo, 3 mo follow-up Country: USA Setting: Pregnancy and addiction outpatient	**(1) MET+TAU**: 3 individual sessions of **Motivational Enhancement Therapy for Pregnant Substance users (MET-PS)** with MET clinician **(1) TAU**: Typical treatment services with at least 3 being individual sessions with a clinician	N=200 pregnant (<32 weeks) adults initiating outpatient treatment for substance use disorder. Rate of primary drug differed across site, ranging from 8% to 50% for cocaine and from 0% to 16% for MA.	**Retention**: NSD bw groups at 1 month (81% overall) or 3-month follow-up (75% overall). **Drug use** (UDT): NSD btw groups in positive urine drug test at 1 month or 3-month follow-up (p=0.75). **Treatment attendance**: NSD bw groups at month 1 or 3-month follow-up. **Readiness to change (URICA):** No change from baseline at 1 month in the MET group, but decreased in the TAU group (MD 0.3 vs -3.7, MD=4 [0.69, 7.31] p=0.02). **Prenatal care visits**: NSD bw groups. Both groups reported significant increases in prenatal care utilization.	In Terplan 2015[5] Cochrane RoB assessment: Unclear No blinding Study had significant site effects between the 3 study sites. Also in Preg BI-MI, Preg Other Psychosocial
Petzold 2021[8]	Cross-sectional Study period: 2016-2019 Germany Outpatient	**(1) Integrated care**: Psychiatric, obstetric, and pediatric departments; local drug counseling and child welfare services	N=87 pregnant women (27) and new parents (57) with MA-related disorders who received psychiatric care through the integrated care program during the study period.	**Early dropout** (before implementation of a care plan): 19% **Late dropout** (partial completion of the program): 32% **Successful completion**: 49% of participants successfully completed the program, defined as mutually agreed program discharge, continuous abstinence, stable housing, financial security, psychosocial functioning, and a support system, and transitioned successfully to community care. **Duration**: Mean 6.7 months. n.s.d. in participation duration bw participants who partially and successfully completed. **Dropout risk factors:** Depression, ADHD	Also in EtDT Preg Other Psychosocial
Plotzker 2022[9]	Cross-sectional 2017 to 2018	N/A	N= 720 people diagnosed with congenital syphilis (CS) during pregnancy	Of 720 birthing parents, 245 (34%) delivered an infant with CS. Although CS was initially associated with MA use (OR 2.1, 95% CI 1.4,	Prenatal care can protect against congenital

			who were interviewed and linked to infants in the California state surveillance system.	3.1) and homelessness (OR 2.5, 95% CI 1.6, 4.0), the addition of prenatal care into a final adjusted model attenuated these associations to not significant.	syphilis among people who are using MA
Wright 2012[10]	Single cohort Study period: 2007-2010 Location: Hawaii Outpatient	**(1) Integrated care:** Harm reduction model of care for pregnant women who use MA at the Perinatal Addiction Treatment Clinic of Hawaii. Model included prenatal and postpartum care, transportation, child-care, social services, family planning, contingency management (first visit, prenatal appointments, group attendance, goal attainment), and addiction medicine.	N= 213 patients, 97 deliveries for women with past or current history of SUD referred from health providers and community advertising. Majority used MA (86% of women who delivered).	**Drug abstinence at delivery** (UDT): Of the 97 deliveries, 96% had negative UDT at the time of delivery. **Preterm delivery**: Of the 103 infants, 12.6% were born preterm, equal to the state and national average. **Post-partum depression** (Edinburgh Post-Partum depression scale): **Initiation of LARC**: 28/97 (29%) of participants initiated long acting reversible contraceptives (LARCs, eg, intrauterine device (IUD) and implant)) after delivery.	Also in EtDT Preg Other Psychosocial, EtDT Preg Contraception

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

The Royal Women's Hospital. *Management of Methamphetamine Dependence in Pregnancy*.; 2017:8. Accessed September 16, 2021. https://thewomens.r.worldssl.net/images/uploads/downloadable-records/clinical-guidelines/drug-and-alcohol-management-methamphetamine-dependence-in-pregnancy_160517.pdf

Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016. https://www.aezq.de/mdb/edocs/pdf/literatur/s3-gl-methamphetamine-related-disorders-long.pdf

McLafferty LP, Becker M, Dresner N, et al. Guidelines for the Management of Pregnant Women With Substance Use Disorders. *Psychosomatics*. 2016;57(2):115-130. doi:10.1016/j.psym.2015.12.001

NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

American College of Obstetricians and Gynecologists. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

American College of Obstetricians and Gynecologists. Substance Abuse Reporting and Pregnancy: The Role of the Obstetrician–Gynecologist. Committee Opinion No. 473. (Reaffirmed 2014). *Obstet Gynecol*. 2011;117:200-201. doi:10.1097/AOG.0b013e31820a6216

ACOG. Cocaine abuse: implications for pregnancy. ACOG Committee opinion: Committee on Obstetrics: Maternal and Fetal Medicine number 81 --March 1990. *Int J Gynaecol Obstet*. 1991;36(2):164-166.

NSWMH. *Nursing and Midwifery Management of Drug and Alcohol Use in the Delivery of Health Care*. New South Wales Ministry of Health; 2020:38.

Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. *Am J Obstet Gynecol*. 2019;221(1):B5-B28. doi:10.1016/j.ajog.2019.03.022

Ordean A, Wong S, Graves L. SOGC Clinical Practice Guideline: No. 349-Substance Use in Pregnancy. *J Obstet Gynaecol Can*. 2017;39(10):922-937. doi:10.1016/j.jogc.2017.04.028

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Carrol 1995[4]: enhanced program (CM, RP, more prenatal classes, childcare) improved grp attendance, gestational age and birth weight; Ackerman 2021[2] systematic review supported need for prenatal care, gender-specific, non-stigmatizing, reinforcing care, using multidisciplinary teams. Ploztker 2022[9]: prenatal care can protect against congenital syphilis among people who are using MA; Petzold 2021[8] integrated care improved numerous outcomes (MA); Burkett 1998[3] Prenatal care can protect against many of the maternal and fetal complications associated with cocaine use during pregnancy. (cocaine). No direct evidence was found regarding providing a referral to primary care. However, given the known benefits of prenatal care, providing a referral is expected to be beneficial.	Guidelines stress using multidisciplinary teams, providing comprehensive prenatal care, and screening for fetal health and complications of pregnancy. Assumes high quality prenatal care is available and accessible to patients.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Studies cited do not report AEs.	No anticipated adverse effects of enhanced prenatal care; however enhanced care models will require resources that may not be available.	☒ None ☐ Small ☐ Moderate ☐ Large

		☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Above supports moderate positive over no negative except availability.		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct research regarding providing a referral, there are known benefits of prenatal care		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	Providers and patients logically would prefer enhanced, integrate care.	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Not direct studies. However, there are known disparities in access	Expect greater effect for marginalized populations	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced

		☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	Most would favor enhanced care, though financial and workforce considerations may temper enthusiasm	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	Access to programs, availability of programs and cost all limit implementation, but long term benefit may outweigh initial costs. Maintaining a list of local referral resources may take time, but should not be unreasonably burdensome. May not be feasible for SUD providers if there is no prenatal care available locally.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Guidelines stress using multidisciplinary teams, providing comprehensive prenatal care, and screening for fetal health and complications of pregnancy. Known complications of fetal health in those using stimulants may warrant higher levels of specialization provided through MFM management.

Subgroup Considerations

None noted

Implementation Considerations

All pregnant patients should be counseled about the pregnancy itself. Women who do not already have a prenatal care provider will need more counseling. The OBGYN will typically make an additional referral to a Maternal/Fetal Medicine specialist where available. This care is offered to most patients with a SUD given the concern for fetal complications which result from maternal substance use, including stimulant use.
When referring a patient, look for embedded prenatal care in SUD treatment programs (eg, as seen in MOUD programs, Medical homes, FQHCs) and SUD programs with specialty care coordinators.

References

1. NSW Health. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. MHDAO 140396. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

2. Ackerman M, Madampage C, Epp LJ, Gartner K, King A. An environmental scan of impacts and interventions for women with methamphetamine use in pregnancy and their children. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2021;155(2):220-238. doi:10.1002/ijgo.13851
3. Burkett G, Gomez-Marin O, Yasin SY, Martinez M. Prenatal care in cocaine-exposed pregnancies. *Obstet Gynecol*. 1998;92(2):193-200. doi:10.1016/s0029-7844(98)00202-6
4. Carroll KM, Chang G, Behr H, Clinton B, Kosten TR. Improving Treatment Outcome in Pregnant, Methadone-Maintained Women: Results From a Randomized Clinical Trial. *Am J Addict*. 1995;4(1):56-59. doi:10.1111/j.1521-0391.1995.tb00259.
5. Terplan M, Ramanadhan S, Locke A, Longinaker N, Lui S. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev*. 2015;(4). doi:10.1002/14651858.CD006037.pub3
6. Kropp F, Winhusen T, Lewis D, Hague D, Somoza E. Increasing prenatal care and healthy behaviors in pregnant substance users. *J Psychoactive Drugs*. 2010;42(1):73-81. doi:10.1080/02791072.2010.10399787
7. Winhusen T, Kropp F, Babcock D, et al. Motivational enhancement therapy to improve treatment utilization and outcome in pregnant substance users. *J Subst Abuse Treat*. 2008;35(2):161-173. doi:10.1016/j.jsat.2007.09.006
8. Petzold J, Spreer M, Krüger M, et al. Integrated Care for Pregnant Women and Parents With Methamphetamine-Related Mental Disorders. *Front Psychiatry*. 2021;12:762041. doi:10.3389/fpsyt.2021.762041
9. Plotzker RE, Burghardt NO, Murphy RD, et al. Congenital syphilis prevention in the context of methamphetamine use and homelessness. *Am J Addict*. Published online March 27, 2022. doi:10.1111/ajad.13265
10. Wright TE, Schuetter R, Fombonne E, Stephenson J, Haning WF. Implementation and evaluation of a harm-reduction model for clinical care of substance using pregnant women. *Harm Reduct J*. 2012;9(1):5. doi:10.1186/1477-7517-9-5

Table 29. Screen Social Services – Pregnancy & Postpartum

Recommendation: Clinicians should incorporate additional elements into the comprehensive assessment of StUD for patients who are pregnant, including:

a. reviewing eligibility criteria for locally available programs that specifically address biopsychosocial needs related to pregnancy and parenting

Clinical Question Summary

Clinical Question	Are there additional social service needs that should be addressed when assessing persons who are pregnant, or is the standard assessment for StUD appropriate and effective?
Population	Pregnant patients being assessed for stimulant use disorder
Intervention	Referral to social services to address biopsychosocial needs
Comparison	TAU
Main Outcomes	Pregnancy outcomes
Setting	Outpatient prenatal care
Background & Definitions	Childcare Transportation Housing Food insecurity (WIC nutrition) Domestic violence, Intimate Partner Violence Notes • "ATS use in pregnancy is associated with poor antenatal care and adverse, short-term social outcomes. Further, women using these drugs are more likely to be unemployed, use other drugs of abuse and have higher rates of domestic violence and adoption when compared to a controlled group, and are more marginalized and more likely to have child protection services being involved in their children's ongoing care. Level of evidence: III-2" (NSWMH, 2014, p. 88)[1]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

NSWMH. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au

Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. *Am J Obstet Gynecol*. 2019;221(1):B5-B28. doi:10.1016/j.ajog.2019.03.022

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

WHO. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. World Health Organization; 2014. Accessed September 16, 2021. https://apps.who.int/iris/handle/10665/107130

NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

ACOG. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No relevant studies, only clinical guidelines that argue wrap-around services will benefit pregnant individuals with StUD.	Seems common sense but no direct support for efficacy.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	No undesirable effects are anticipated.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence; universal support in clinical guidelines balanced only against financial and workforce limitations.		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence	Seems common sense, but if provision of these services draws resources away form other treatment services, may not be as beneficial as guidelines suggest.	☒ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☐ High
*** Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	Both providers and patients almost certainly would favor provision of wraparound services.	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
*** Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	The disadvantaged have more need for wraparound services, and thus referral of such should enhance equity. This assumes that services are available and accessed.	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies

* **Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	Both providers and patients almost certainly would favor provision of wraparound services.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
* **Feasibility**: Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	Current healthcare system poorly set up to coordinate and provide for such services; immediate impact of such wraparound services not supported financially or by workforce; in the long-run such services *should* prove financially beneficial and if workforce can be trained, improve workforce morale.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Clinical guidance and general consensus strongly favor facilitating wraparound psychosocial services for those with StUDs.

Subgroup Considerations

Minoritized populations have the greatest need for such services, and so are more likely to benefit. However, also potentially less likely to be available to these populations.

Implementation Considerations

Immediate financial need to provide services; lack of workforce to deliver such services (need case managers, greater social work need, etc.

References

1. NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

Table 30. Screen Factors Pregnancy

Recommendation: When screening for acute issues, complications, and sequalae associated with stimulant use in patients who are pregnancy, clinicians should pay particular attention to factors impacting pregnancy and fetal development.

Clinical Question Summary

Clinical Question	Are there additional health conditions that should be evaluated in persons who are pregnant, or is the standard assessment for StUD appropriate and effective?
Population	Pregnant patients being assessed for stimulant use disorder
Intervention	Screening for factors impacting pregnancy outcomes
Comparison	TAU
Main Outcomes	Pregnancy outcomes
Setting	Outpatient prenatal clinic
Background & Definitions	Notes • "The impact of different substances at different stages of pregnancy is complex. Risk varies depending on the amount, type, frequency and pattern of AOD use, as well as individual maternal characteristics." (NSWMH 2021, p. 24)[1] • "Women who have used substances during pregnancy may be at increased risk of postnatal depression." (NSWMH, 2021, p. 25)[1] • "The use of cocaine may be associated with increased exposure to HIV, hepatitis and syphilis from intravenous drug use and unprotected intercourse with multiple partners." (NSWMH 2014, p. 90)[2]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Existing Guidelines

ACOG. Cocaine abuse: implications for pregnancy. ACOG Committee opinion: Committee on Obstetrics: Maternal and Fetal Medicine number 81 --March 1990. *Int J Gynaecol Obstet*. 1991;36(2):164-166.

American College of Obstetricians and Gynecologists. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

NSWMH. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au

Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. *Am J Obstet Gynecol*. 2019;221(1):B5-B28. doi:10.1016/j.ajog.2019.03.022

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Based on guideline consensus; strong support of screening for blood-born pathogens, STIs, depression and nutritional deficiencies in those using stimulants. No direct studies cited.		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	Patients being asked about depression and suicidality – no evidence of harm there.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies	With the caveat of understanding reporting laws, this screening is standard medical care regardless of stimulant use. It is particularly important in the stimulant using population because there are at higher risk.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies

		☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	High degree of consensus in existing guidelines.	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences**: Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
Based on guidelines, provider value for detection of infections, nutritional deficiencies, mental health conditions is high.		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
*** Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	Given the conditions for which screening is recommended afflict the disadvantaged more than non-minoritized patients, equity should be enhanced by screening. Should reduce inequities	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies
*** Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct studies.	Some patients may not want deficiencies detected; must be aware of reporting issues.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
Not direct studies.	It is current standard practice, so it is feasible. Would need economic analysis and field-testing analysis for feasibility.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Based on guideline consensus; strong support of screening for blood born pathogens, STIs, depression and nutritional deficiencies in those using stimulants. Will reduce failure to detect common co-morbidities of StUDs in pregnant population.

Subgroup Considerations

May be more necessary in those who access primary and obstetrical care less, eg, the minoritized.

Implementation Considerations

- All pregnant patients should be counseled about the pregnancy itself. Women who do not already have a prenatal care provider will need more counseling.
- PCPs/Ob/Gyns already very burdened by how short a time they have with patient's - uptake of more screening may be poor.

Research Priorities

Is there an efficient way to improve such screening in PCP/Ob/Gyn practice.

References

1. NSWMH. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au
2. NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

Table 31. Pharmacotherapy – Pregnancy & Postpartum

Recommendation: Risk versus benefit to the fetus or infant should be considered when medications are used to manage StUD, stimulant intoxication, or stimulant withdrawal.

Clinical Question Summary

Clinical Question	What additional consideration should be included when considering pharmacotherapy for stimulant intoxication, withdrawal, or use disorder in persons who are pregnant or breastfeeding?
Population	Patients with stimulant intoxication, withdrawal, or use disorder who are pregnant or patients with StUD who are breastfeeding
Intervention	Any pharmacotherapy used for treating the signs and symptoms of stimulant intoxication, withdrawal, or use disorder
Comparison	No pharmacological treatment or other pharmacological treatment
Main Outcomes	Stimulant use, treatment retention, symptom reduction, pregnancy outcomes, harm to fetus or infant
Setting	Prenatal clinic
Background & Definitions	Risks and benefits need to be carefully weighed when considering medications for StUD, or stimulant intoxication or withdrawal
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Harm to fetus or infant	N/A	Systematic review: Rayburn & Bogenschutz 2004[1] (Not assessed)	• Pharmacotherapy for pregnant women with addictions. • Clinical experience with anti-addictive medications in stimulant using pregnant women is very limited. • Among medications with trials demonstrating effectiveness in managing stimulant withdrawal or use disorder: ○ Amantadine, dopamine agonists, and lithium are not recommended during pregnancy without clinical trials • Among medications with trials demonstrating effectiveness in managing other substance withdrawal or use disorders, that are also used for stimulant use withdrawal or disorder:	Many studies confounded by polysubstance use, especially alcohol, which may explain detected abnormalities.

			○ Bupropion: Animal studies have not found an association between bupropion use and congenital defects. ○ Naltrexone: Animal studies have not found an association between naltrexone use and congenital malformation, but there is evidence for altered behavior through the facilitation of sexual behaviors in exposed male rats. "A preliminary study by Hulse et al[48] of 26 women with variable exposure to naltrexone did not detect any gross abnormalities in fetal development." (Rayburn and Bogenschutz, 2004, p. 1889) ○ Diazepam for intox and withdrawal: Prospective and retrospective clinical trials have not found an association between diazepam use and birth defects. ○ Clonidine: for inpatient detoxification to treat autonomic signs (tachycardia, elevated blood pressure, agitation), while monitoring for sedation and hypotension. Clinical studies of pregnant women receiving clonidine for hypertension during the second and third trimesters have not found an association significant adverse fetal effects. • "As with all medications taken during pregnancy, the decision to prescribe an antiaddictive medication must be guided after the benefits are weighed with potential risks, based on clinical acumen and limited outcomes information. To qualify for antiaddictive pharmacotherapy, patients must meet criteria for dependence on the substance in question. In addition, there must be no contraindication to the medication, and the patient must understand the risks and benefits of its use." (Rayburn and Bogenschutz, 2004, p. 1887) • "In general, the dosing regimen of each drug would be the same for pregnant women as for others, with use of the lowest effective dose for each individual's needs." (Rayburn and Bogenschutz, 2004, p. 1887) • "Virtually all antiaddiction medications are thought to pass into breast milk.[10] Although the concentration may be low, exposure to the breast-feeding infant with prolonged daily dosings would be unsafe. A commonly asked question about breast-feeding is ''Which would be safer, the known exposure to an antiaddictive medication or the uncertainty of exposure to an abused substance?'' In our experience, very few women with continued illicit drug use wish to breast-feed." (Rayburn and Bogenschutz, 2004, p. 1887)	

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Comments
Yonkers 2014[2]	RCT Duration: 12 wks Country: US Setting:	Progesterone	N=50		

Existing Guidelines

The Royal Women's Hospital. *Management of Methamphetamine Dependence in Pregnancy*.; 2017:8. Accessed September 16, 2021. https://thewomens.r.worldssl.net/images/uploads/downloadable-records/clinical-guidelines/drug-and-alcohol-management-methamphetamine-dependence-in-pregnancy_160517.pdf

WHO. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. World Health Organization; 2014. Accessed September 16, 2021. https://apps.who.int/iris/handle/10665/107130

ACOG. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*

• No **direct** evidence of efficacy and safety for treatment of StUD in pregnant patients.
• Evidence is for non-pregnant StUD patients
• Evidence is for Pregnant SUD patients, primarily OUD
• Contraindicated in pregnancy –
  o Medications that are studied in the general pop are category C, except bupropion
  o Bupropion (Category B – No risks in animal studies, but no human studies))
  o Mirtazapine not enough information (category C)
  o For category B & Cs, generally a risk-benefit conversation w/ doctor: benefit of avoiding continued use vs risk to fetus)
  o No know known risks, but no known safety
	Risks also often vary by trimester, but the CGC will try to reduce complexity by judging across whole pregnancy period.
	
	Intoxication and withdrawal should be treated. Desirable effects will VARY depend on severity of signs and symptoms being treated.
	
	Maintenance treatment – In non-pregnant patients, effect on reducing stimulant use VARIES from small to moderate.
		☐ None
		☐ Small
		☐ Moderate
		☐ Large
		☒ Varies
		☐ Don't know

• None are contraindicated while breastfeeding (even Adderall not contraindicated, is a risk-benefit conversation w/ doctor) • **BZDs & other GABAergic agents** – None are indicated in pregnancy, but would use in intoxicated psychotic patient because less harm than not treating symptoms. Don't use phenobarbital. • Otherwise, for antipsychotics and "unit-based sedatives aka ICU" consult with multi-disciplinary team. Haloperidol is contraindicated. Category C: Haloperidol. Quetiapine and olanzapine "No information"		
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Clinical judgement would indicate add'l risk of medications to fetus; risk of resp. suppression in newborns with benzodiazepines; no support for maintenance Category C: not enough information about effects		☐ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Treatment of intoxication and withdrawal based on clinical judgment, none for maintenance If co-occurring OUD, see OUD guidelines for those meds.		☐ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☒ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Low certainty evidence for usual treatments in pregnancy for intoxication and withdrawal; no support for medications for StUD treatment for maintenance, but yes for OUD	This applies to tx of OUD	☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Treating intoxication, withdrawal, reducing continued stimulant use is likely valued consistently. Values and preferences on potential undesirable effects of medications used to produce primary outcomes might vary.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No direct evidence	Improving function in those with SUDs should differentially affect those with StUDs	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Both providers and patients will have very different views on the use of medications while pregnant	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	May be lack of access	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Because no direct evidence exists for using pharmacotherapy for treatment of StUD, or stimulant intoxication/withdrawal, careful consideration of risks and benefits should be done when considering medication

Subgroup Considerations

None noted

Implementation Considerations

- Unless an OB, SUD treatment providers should work collaboratively with patient and OB team to weigh risk/benefit of medications
- In acute intoxication, consult with pharmacy and/or critical care to weigh risk/benefit of medications

Research Priorities

- Huge need for research in this area

References

1. Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *Am J Obstet Gynecol*. 2004;191(6):1885-1897. doi:10.1016/j.ajog.2004.06.082
2. Yonkers KA, Forray A, Nich C, et al. Progesterone for the reduction of cocaine use in post-partum women with a cocaine use disorder: a randomised, double-blind, placebo-controlled, pilot study. *Lancet Psychiatry*. 2014;1(5):360-367. doi:10.1016/S2215-0366(14)70333-5

Table 32. Prenatal Care Incentives

Recommendation: Clinicians should consider contingency management (CM) to incentivize attendance at prenatal appointments, if feasible, in addition to the usual targets of CM (eg, stimulant abstinence).

Clinical Question Summary

Clinical Question	What are the most effective and appropriate interventions for increasing prenatal care access and attendance in patients being treated for StUD?
Population	Pregnant patients being assessed for stimulant use disorder
Intervention	CM to incentivize attendance at prenatal appointments
Comparison	TAU
Main Outcomes	Prenatal care and Pregnancy outcomes (indirect)
Setting	Outpatient prenatal clinic
Background & Definitions	Notes • "ATS use in pregnancy is associated with poor antenatal care and adverse, short-term social outcomes. Further, women using these drugs are more likely to be unemployed, use other drugs of abuse and have higher rates of domestic violence and adoption when compared to a controlled group, and are more marginalised and more likely to have child protection services being involved in their children's ongoing care. Level of evidence: III-2" (NSWMH 2014, p. 88)[1]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **n.s.d.:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Prenatal care visits	N/A	Systematic review: Washio 2021[2] (Not assessed)	Mixed evidence from 3 RCTs that contingency management is effective in improving prenatal care visit attendance. Includes non-SUD population studies. **Incentives** increased prenatal visit attendance in 1 study • Melnikow 1997 (Non-SUD population) **Trend for incentives** to increase prenatal visit attendance in 1 study • Elk 1998 (CoUD, CM+TAU vs TAU)	Prospective studies on incentives contingent on maternal health behavior change

			No sig difference in prenatal care attendance in 1 study • Laken and Ager 1995 (Non-SUD population)	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Elk 1995[3]		Incentive for attending substance use disorder treatment and prenatal clinic appointments thrice weekly		overall high compliance with prenatal care	In Hand 2017[4]
Elk 1998[5]	RCT Duration: 4–26 weeks during pregnancy USA Outpatient	**(1) CM + TAU**: Incentive for abstinence (3 consecutive drug free urine samples in a one-week period) and attendance at prenatal visits **(2) TAU**: All received prenatal care, drug counselling, nutritional education, and HIV counselling.	N=12 pregnant cocaine-dependent (DSM-III-R) women who reported having used cocaine during the current pregnancy but had ceased use more than 30 days prior to entering the study	**Retention:** n.s.d. **Cocaine use** (UDT): n.s.d. in abstinence between groups **Attendance at prenatal visits**: Trend towards better attendance in CM + TAU group (100% vs 83%, p=0.077) **Dependence severity** (ASI): n.s.d. **Adverse perinatal outcomes** (premature rupture of the membranes, preterm labor, preterm birth, low birth weight): Lower rate in CM + TAU (0% vs 67%, p=0.022)	In Terplan 2015[6] Risk of bias assessment: Unclear; Washio 2021[2]; Hand 2017[4]
Kropp 2010[7] secondary analysis of Winhusen 2008[8]	RCT Duration: 1 mo, 3 mo follow-up Country: USA Setting: Pregnancy and addiction outpatient	**(1) MET+TAU**: 3 individual sessions of **Motivational Enhancement Therapy for Pregnant Substance users (MET-PS)** with MET clinician **(1) TAU**: Typical treatment services with at least 3 being individual sessions with a clinician	N=200 pregnant (<32 weeks) adults initiating outpatient treatment for substance use disorder. Rate of primary drug differed across site, ranging from 8% to 50% for cocaine and from 0% to 16% for MA.	**Prenatal care visits**: NSD bw groups. Both groups reported significant increases in prenatal care utilization. **Readiness to change (URICA):** No change from baseline at 1 month in the MET group, but decreased in the TAU group (MD 0.3 vs -3.7, MD=4 [0.69, 7.31] p=0.02). **Other outcomes**: NSD in Retention, Drug use (UDT), or Treatment attendance at 1 month or 3-month follow-up	In Terplan 2015[6] Cochrane RoB assessment: Unclear No blinding Study had significant site effects between the 3 study sites. Also in Preg BI-MI, Preg Other Psychosocial

Wright 2012[9]	Single cohort Study period: 2007-2010 Location: Hawaii Outpatient	**(1) Integrated care:** Harm reduction model of care for pregnant women who use MA at the Perinatal Addiction Treatment Clinic of Hawaii. Model included prenatal and postpartum care, transportation, child-care, social services, family planning, contingency management (first visit, prenatal appointments, group attendance, goal attainment), and addiction medicine.	N= 213 patients, 97 deliveries for women with past or current history of SUD referred from health providers and community advertising. Majority used MA (86% of women who delivered).	**Drug abstinence at delivery** (UDT): Of the 97 deliveries, 96% had negative UDT at the time of delivery. **Preterm delivery**: Of the 103 infants, 12.6% were born preterm, equal to the state and national average. **Post-partum depression** (Edinburgh Post-Partum depression scale): **Initiation of LARC**: 28/97 (29%) of participants initiated long acting reversible contraceptives (LARCs, eg, intrauterine device (IUD) and implant)) after delivery.	Also in EtDT Preg Other Psychosocial, EtDT Preg Contraception

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

McLafferty LP, Becker M, Dresner N, et al. Guidelines for the Management of Pregnant Women With Substance Use Disorders. *Psychosomatics*. 2016;57(2):115-130. doi:10.1016/j.psym.2015.12.001

NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

ACOG. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

American College of Obstetricians and Gynecologists. Substance Abuse Reporting and Pregnancy: The Role of the Obstetrician–Gynecologist. Committee Opinion No. 473. (Reaffirmed 2014). *Obstet Gynecol*. 2011;117:200-201. doi:10.1097/AOG.0b013e31820a6216

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence for the effect of contingency management on prenatal care participation is mixed. Studies have found both increased rates of attendance or no significant effect. Two low quality studies showed a slight increase	Prenatal care has been shown to reduce negative effects of the substance abuse during pregnancy, and so desirable effects of increasing prenatal care attendance are likely large. The effect of CM on this outcome was small, so the desirable effect of the intervention was determined to be moderate.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	It is more feasibility than any undesirable effects	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	Although no undesirable effects	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies

***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Women's health and obstetrics is an area where health inequity is visibly seen. Improvement in prenatal care in any stigmatized population can improve this in some cases	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Most would find increasing prenatal care as acceptable. Many, particularly governmental regulations or payers, may not accept certain incentives for care.	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	CM is not available in many areas of care.	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Regular prenatal care improves pregnancy outcomes. Although studies are mixed, there is some evidence, although low quality, that shows improved prenatal care attendance with the use of CM.

Subgroup Considerations

None noted

Implementation Considerations

CM is not widely available across all care environments and often time state legislation can prove to be a barrier to effective CM.

References

1. NSW Health. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. MHDAO 140396. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au
2. Washio Y, Atreyapurapu S, Hayashi Y, et al. Systematic review on use of health incentives in U.S. to change maternal health behavior. *Prev Med*. 2021;145:106442. doi:10.1016/j.ypmed.2021.106442
3. Elk R, Schmitz J, Spiga R, Rhoades H, Andres R, Grabowski J. Behavioral treatment of cocaine-dependent pregnant women and TB-exposed patients. *Addict Behav*. 1995;20(4):533-542. doi:10.1016/0306-4603(94)00076-B
4. Hand DJ, Ellis JD, Carr MM, Abatemarco DJ, Ledgerwood DM. Contingency management interventions for tobacco and other substance use disorders in pregnancy. *Psychol Addict Behav*. 2017;31(8):907-921. doi:10.1037/adb0000291
5. Elk R, Mangus L, Rhoades H, Andres R, Grabowski J. Cessation of cocaine use during pregnancy: effects of contingency management interventions on maintaining abstinence and complying with prenatal care. *Addict Behav*. 1998;23(1):57-64. doi:10.1016/s0306-4603(97)00020-8
6. Terplan M, Ramanadhan S, Locke A, Longinaker N, Lui S. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev*. 2015;(4). doi:10.1002/14651858.CD006037.pub3
7. Kropp F, Winhusen T, Lewis D, Hague D, Somoza E. Increasing prenatal care and healthy behaviors in pregnant substance users. *J Psychoactive Drugs*. 2010;42(1):73-81. doi:10.1080/02791072.2010.10399787
8. Winhusen T, Kropp F, Babcock D, et al. Motivational enhancement therapy to improve treatment utilization and outcome in pregnant substance users. *J Subst Abuse Treat*. 2008;35(2):161-173. doi:10.1016/j.jsat.2007.09.006
9. Wright TE, Schuetter R, Fombonne E, Stephenson J, Haning WF. Implementation and evaluation of a harm-reduction model for clinical care of substance using pregnant women. *Harm Reduct J*. 2012;9(1):5. doi:10.1186/1477-7517-9-5

Table 33. Postpartum Care

Recommendation: Clinicians should consider providing additional treatment support around the time of birth as the post-partum period may be a time of increased stress and risk of return to stimulant use.

Clinical Question Summary

Clinical Question	Are there additional treatment needs for patients with stimulant use disorder in the postpartum period? For patients with any level of stimulant use?
Population	Patients who use stimulants nonmedically or with stimulant use disorder who are about to or recently gave birth
Intervention	Additional postpartum support
Comparison	TAU
Main Outcomes	Stimulant use outcomes
Setting	Outpatient prenatal clinic, home-based
Background & Definitions	Notes • The postpartum period includes several unique risk factors (eg, sleep deprivation, mood disturbances, increased stress) for StUD treatment non-adherence and relapse • "Even for women who achieve and maintain abstinence while pregnant, postpartum substance use relapse is common within the first 6 to 12 months after delivery." Prince & Ayers 2022[1] • For opioid use disorder, "postpartum relapses occur more frequently than antepartum." Prince & Ayers 2022[1] • Martinez A, Allen A. A review of nonpharmacological adjunctive treatment for postpartum women with opioid use disorder. *Addict Behav*. 2020;105:106323. https://doi.org/10.1016/j.addbeh.2020.106323
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Comments
Forray 2015[2]				By three months postpartum, 27% (6/22) of women who achieved abstinence from	

				cocaine during pregnancy relapsed. By two years post-delivery, 41% (9/22) of women who achieved abstinence from cocaine relapsed (HR 0.38, 95% CI 0.16-0.92, p=0.032).	
Salisbury 2007[3]		4 National Institute of Child Health and Human Development Neonatal Research Network sites	385 new mothers who used cocaine prenatally and 668 demographically matched new mothers who did not at one month postpartum (80% Black; 13% White; 7% Other)	**Postpartum depression**: 19.3% of cocaine exposed women had symptoms of postpartum depression **Cocaine use**: Prenatal cocaine users with depressive symptoms were significantly more likely than those without depressive symptoms to report postpartum cocaine use (26.3% vs. 14.3%)	Depression was determined as a serious depression lasting ≥ 2 weeks in the past 30 days and a score of ≥ 3 for psychological problems on the Addiction Survey Index (ASI) In Chapman & Wu 2013[4]

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

NSWMH. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au

Ecker J, Abuhamad A, Hill W, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine. *Am J Obstet Gynecol*. 2019;221(1):B5-B28. doi:10.1016/j.ajog.2019.03.022

ACOG. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Prince & Ayers 2022[1]	**Substance Use In Pregnancy** Evaluation of Perinatal Depression: • "During the evaluation of females throughout pregnancy, both with and without substance use disorders, it is recommended to routinely screen pregnant and postpartum women for depression. Direct evidence, studied and reported on by the United States Preventive Services Task Force (USPTF),	

	suggests screening pregnant and postpartum women for depression may reduce depressive symptoms in women and reduce the prevalence of depression in a given population. Even in settings where there is a lack of specialty treatment resources such as treatment protocols, care management, and the availability of specially trained psychiatric clinicians, evidence still supports screening for depression in pregnant and postpartum women.[19]" • "ACOG, in its most recent committee opinion, recognizes that screening alone for perinatal depression can have clinical benefits, with maximal benefit achieved with the initiation of treatment or referral to mental health providers. Edinburgh Postnatal Depression Scale (EPDS) is well-studied in research settings and has been translated into 50 different languages, with ten self-reported questions that are health literacy appropriate.[20]"	
Gopman 2014[5]	**Prenatal and Postpartum Care of Women with Substance Use Disorders** • "Postpartum depression, which occurs more frequently among women with substance abuse disorders,[61] may be another risk factor for relapse.[62]" (p. 222) o [61] Holbrook A, Kaltenbach K. Co-occurring psychiatric symptoms in opioid-dependent women: the prevalence of antenatal and postnatal depression. Am J Drug Alcohol Abuse 2012;38(6):575–9. o [62] Chapman SL, Wu LT. Postpartum substance use and depressive symptoms: a review. Women Health 2013;53(5):479–503. • "Close follow-up, including an early postpartum clinic visit at 1 to 2 weeks after delivery, is recommended." (p. 222) • "At this visit, a formal assessment for postpartum depression, such as the Edinburgh Postnatal Depression Scale, can be administered, and clinicians should ask directly about drug cravings and relapse to substances of abuse." (p. 222)	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Cocaine related studies showed 27% and 41% return to use after 3 months and 2 years respectively (small study) Increased risk PP depression. Depression identified as increased risk factor for return to use		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	No expectation enhanced post-partum care would be harmful	☒ None ☐ Small

		☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Although low quality data, benefits of enhanced support postpartum are important outcomes	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Small sample		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Known health inequity for minoritized populations at greater risk of poor post-partum care access	Increased monitoring should reduce existing inequity as long as access to care results	☐ Increased ☐ Probably increased ☐ Uncertain

		☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Access to care continues to remain a concern	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Although low quality studies, there is some evidence that the postpartum period may show increased rates of return to use. There is also nearly a 20% chance of developing post-partum depression and depression has been linked to higher rates of return to use.

Subgroup Considerations

None noted

Implementation Considerations

Access to care both antenatally and post-partum continue to be problematic with health inequities identifying in diagnosing and appropriately managing post-partum depression in marginalized populations

Increased treatment support could include

- Increased behavioral intervention
- More frequent

References

1. Prince MK, Ayers D. Substance Use In Pregnancy. In: *StatPearls*. StatPearls Publishing; 2022. Accessed January 24, 2023. http://www.ncbi.nlm.nih.gov/books/NBK542330/
2. Forray A, Merry B, Lin H, Ruger JP, Yonkers KA. Perinatal substance use: a prospective evaluation of abstinence and relapse. *Drug Alcohol Depend*. 2015;150:147-155. doi:10.1016/j.drugalcdep.2015.02.027
3. Salisbury AL, Lester BM, Seifer R, et al. Prenatal cocaine use and maternal depression: Effects on infant neurobehavior. *Neurotoxicol Teratol*. 2007;29(3):331-340. doi:10.1016/j.ntt.2006.12.001
4. Chapman SLC, Wu LT. Postpartum Substance Use and Depressive Symptoms: A Review. *Women Health*. 2013;53(5):479-503. doi:10.1080/03630242.2013.804025
5. Gopman S. Prenatal and Postpartum Care of Women with Substance Use Disorders. *Obstet Gynecol Clin North Am*. 2014;41(2):213-228. doi:10.1016/j.ogc.2014.02.004

Table 34. Breastfeeding

Recommendation: Clinicians should educate patients who use stimulants on the risks of stimulant use while breastfeeding and counsel patients not to breastfeed if they are actively using stimulants (except as prescribed).

Clinical Question Summary Table

Clinical Question	1. Should patients with a stimulant use disorder breastfeed? 2. When can a patient who uses stimulants safely breastfeed? 3. Can clinicians increase the rate of safe breastfeeding in patients with a stimulant use disorder? With any stimulant use?
Population	Pregnant or postpartum women who use stimulants non-medically, with or without stimulant use disorder
Intervention	Intervention for breastfeeding
Comparison	Not encouraging breastfeeding (treatment-as-usual), discouraging breastfeeding (recommending breast milk substitutes), or recommending short-term use of breast milk substitutes for periodic substance use.
Main Outcomes	Breastfeeding rate, breastfeeding frequency
Setting	Any clinical setting
Background & Definitions	Notes: • Literature on stimulant transmission into breast milk is sparse and primarily consist of case studies. Most clinical trials have been done for alcohol and opioid maintenance medications. • "Drugs with long half lives are more likely to accumulate in human milk, and drugs with high bioavailability are more easily absorbed by the infant (Hale, 2004)" (WHO 2014, p. 128)[1]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MMT**: Methadone maintenance therapy, **MaUD**: Methamphetamine use disorder, **N**: Number, **n.s.d.:** No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Breastfeeding	N/A	Systematic review: Washio 2021[2] (Not assessed)	High certainty of evidence from 3 RCTs with 139 participants that **incentives** are effective in improving rates of breastfeeding. However, no studies were in SUD populations. • Finch & Daniel, 2002; Sciacca 1995; Washio 2017a	Prospective studies on incentives contingent on maternal health behavior change

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

No individual studies published after the most recent systematic review or meta-analysis found in the literature review.

Existing Guidelines

NSWMH. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Ordean A, Wong S, Graves L. SOGC Clinical Practice Guideline: No. 349-Substance Use in Pregnancy. *J Obstet Gynaecol Can*. 2017;39(10):922-937. doi:10.1016/j.jogc.2017.04.028

The Royal Women's Hospital. *Management of Methamphetamine Dependence in Pregnancy*.; 2017:8. Accessed September 16, 2021. https://thewomens.r.worldssl.net/images/uploads/downloadable-records/clinical-guidelines/drug-and-alcohol-management-methamphetamine-dependence-in-pregnancy_160517.pdf

McLafferty LP, Becker M, Dresner N, et al. Guidelines for the Management of Pregnant Women With Substance Use Disorders. *Psychosomatics*. 2016;57(2):115-130. doi:10.1016/j.psym.2015.12.001

Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

NSWMH. *Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period*. New South Wales Ministry of Health; 2014. Accessed September 16, 2021. www.health.nsw.gov.au

WHO. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. World Health Organization; 2014. Accessed September 16, 2021. https://apps.who.int/iris/handle/10665/107130

ACOG. Methamphetamine Abuse in Women of Reproductive Age. Committee Opinion No. 479. (Reaffirmed 2021). *Obstet Gynecol*. 2011;117:751-755. doi:10.1097/AOG.0b013e318214784e

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence of benefit in active stimulant use; if abstinence achieved, then benefit of breastfeeding assumed same as for non-StUD population. Milk passage of stimulants that guideline consensus argues results in harm to baby	If binge use, 24 hrs wait until consider breast-feeding. Given contamination in the drug supply, also consider testing supply for or presuming the presence of fentanyl.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies

Desirable effects = avoiding exposure of newborn to stimulants While there is no known data for outcomes in newborn, stimulants are passed to breastmilk. Out of an abundance of caution, it is expected that avoiding exposure		☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Would not get the known benefits to mother and infant of breastfeeding.	However, there are effective alternatives. formula feeding	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
No – because no evidence supporting benefit	Common sense is that the intervention is somewhat favored	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	All major guidelines recommend against breastfeeding in active use	☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
Most would favor protecting the baby.	Using mothers may argue psychological distress of not being able to breastfeed.	☐ Yes

		☐ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☒ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Breastfeeding has been found to have numerous benefits to mom and baby, however levels of stimulants in breastmilk have been found to be high with the potential to infer harm to baby. The committee recommends against breastfeeding in those women who are actively using stimulants. Proper education and

counseling should be completed regarding risks of stimulants in breastmilk. Support and education should be provided for the woman who has achieved sustained abstinence from stimulant use that desires breastfeeding.

Subgroup Considerations

None noted

Implementation Considerations

No clear barriers to implementation of recommendations.

Research Priorities

Does recommending against breastfeeding in those using psychostimulants result in reduced breast-feeding.

References

1. WHO. *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy*. World Health Organization; 2014. Accessed September 16, 2021. https://apps.who.int/iris/handle/10665/107130
2. Washio Y, Atreyapurapu S, Hayashi Y, et al. Systematic review on use of health incentives in U.S. to change maternal health behavior. *Prev Med*. 2021;145:106442. doi:10.1016/j.ypmed.2021.106442

Additional Population Considerations

Table 35. Sexual and Gender Minoritized individuals

Recommendation: Clinicians should consider referring SGM patients with StUD to SGM affirming programs when their history or behavior suggest that they may not be comfortable fully participating in a general population setting (eg, distress related to their identities, difficulty discussing drug related sexual activities, inner conflicts, trauma history, etc.).

Clinical Question Summary Table

Clinical Question	1. What are the most effective and appropriate interventions for the treatment of StUD in SGM patients? 2. Should SGM patients with StUD be referred to SGM-focused programs? 3. What additional consideration should clinicians have when evaluating and treating stimulant use disorder in SGM patients?
Population	MSM, LGBT-identifying patients with stimulant use disorder
Intervention	Pharmacological, psychosocial, harm reduction
Comparison	TAU or other comparator
Main Outcomes	Substance use, risky sexual behavior
Setting	Setting varies depending on intervention
Background & Definitions	Notes: <u>Stimulant use</u> • Sexual minority women experience increased rates of stimulant use compared with their heteronormative counterparts (Philbin et al., 2020). (SAMHSA 2021, p131)[1] • "Using NSDUH data, a 2021 study evaluating prescription drug misuse by sexual identity found that men who identified as gay or bisexual had higher rates of past-year prescription stimulant misuse (5.1% and 6.4%, respectively) compared with men who identified as heterosexual (2.3%; M. Diaz et al., 2021)." (SAMHSA 2021, p 135)[1] • "Results from these studies show cocaine and amphetamine use is somewhat more common among transgender people than cisgender people, with past-year cocaine use among transgender people an estimated 6.8 percent higher and past-year amphetamine use an estimated 1.3 percent higher (Scheim et al., 2017)." (SAMHSA 2021, p139)[1] <u>Stimulant use disorder</u> • Among 8,872,793 VA outpatients from 10/1/09-7/31/17, transgender patients (8,619, 0.1%) were more likely than cisgender patients to have any drug use disorder (7.2% vs 3.9%, Chi-square=259.6, p<0.001; Adjusted Odds Ratio [aOR] 1.67, 95% CI 1.53-1.83, p<0.001)), amphetamine (1.1% vs 0.3%, Chi-square=159, p<0.001; aOR 2.22, 95% CI 1.82-2.70, p<0.001)), cocaine (1.5% vs 1.1%, Chi-square=12.2, p<0.001; aOR 1.59, 95% CI 1.29-1.95, p<0.001)), and cannabis (3.4% vs 1.5%, Chi-square=208.8, p<0.001; aOR 1.82, 95% CI 1.62-2.05, p<0.001)) use disorders documented in their HER (Frost 2021)[2]. Analysis adjusted for age, race/ ethnicity and fiscal year. While there was no significant difference between transgender and cisgender patients in the likelihood of opioid (aOR 1.09, p=0.384) or sedative (p=0.063) use disorder diagnosis, there was a significant difference in unadjusted prevalence rates of opioid use disorder (1.5% vs 1%, Chi-square=18.2, p<0.001) and

	sedative use disorder (0.3% vs 0.2%, Chi-square=13, p<0.001). Transgender patients were more likely than cisgender patients to be younger (mean age 52 years vs. 61 years, p<0.001) and non-Hispanic white (77% vs. 72%, p<0.001)). Having a past-year mental health condition was twice as common among transgender patients (61% vs. 30%, p<0.001)), but was not a significant interaction with diagnosis in models. • The prevalence of SUD diagnosis was significantly elevated among US transgender adults relative to their cisgender peers including for cocaine use disorder (0.5% vs 0.1%, p<0.001) (Hughto 2021)[3] <u>Other risks</u> • "People who identify as transgender have a higher risk for verbal, physical, and sexual victimization and frequently encounter interpersonal and structural discrimination (Keuroghlian et al., 2015). A national survey of transgender individuals found that 28 percent of individuals delayed medical care because of discrimination and barriers (J. M. Grant et al., 2011):" (SAMHSA 2021, p140)[1] <u>Treatment engagement</u> • "A 2017 literature review that analyzed fndings from the United States, the United Kingdom, and Australia suggests that SUD treatment rates among MSM are likely much lower than they are among men who identify as heterosexual and do not engage in sex with other men (Bourne & Weatherburn, 2017)." (SAMHSA 2021, p136)[1] • "Hypersexuality, sexual assault, and diverse sexual behaviors and partners in the context of stimulant use may result in concerns about sexual identity (Lyons et al., 2010; Ritchwood et al., 2016)." (SAMHSA 2021, p104)[1] • "A lack of specialty SUD care for MSM may be a major deterrent, as clinicians not trained in working with this population may not understand the unique challenges facing some MSM and the sociocultural issues that may contribute to substance use among them (Bourne & Weatherburn, 2017)." (SAMHSA 2021, p136)[1] • "Data from several studies from the 2000s suggest that approximately 50 percent of transgender individuals with SUDs do not seek treatment because of concerns about stigma (Matsuzaka, 2018). When Treatment for Stimulant Use Disorders seeking inpatient SUD care, TGNB people encounter structural barriers, such as gender-segregated treatment facilities, institutional bias, and stigmatizing attitudes among providers (Matsuzaka, 2018)." (SAMHSA 2021, p140)[1] <u>Barriers</u> • "our finding regarding sexualized methamphetamine use shows that SGMSM [sexual and gender minority men who have sex with men] who participate in PnP ["Party 'n' Play"] culture face barriers to substance use supports access. Given that sexualized drug use is an important setting for social connectedness and sexual expression, participants may fear loss of social connection with their friends or loss of their sexual subculture and identity if they reduce or quit using methamphetamine [45]. It is important to note that sex is an important way for SGMSM to form social connections and friendships, and that PnP is a setting where this can occur, given the effects that drugs such as methamphetamine have on feelings of pleasure and connectedness [46]. Of course, these benefits do not necessarily negate harms may arise from PnP use. Indeed, we observed that greater frequency of use was associated with more frequent sexualized methamphetamine use. These deterrents in accessing care may be heightened by the stigmatization that exists between SGMSM services towards people who inject drugs (PWID) and vice versa [44]. This territorial stigmatization has been identified as a barrier to accessing healthcare. As a result, SGMSM who use methamphetamine may feel excluded from both services exacerbating inequalities in accessing support. It is essential that services that prioritize support for certain groups (eg, for PWID or SGMSM) support and engage with each other to increase ease of access. This has implications for how support services are designed and located. Inclusive services that

	acknowledge the important role that sex plays in social connectedness for the SGMS M community may provide opportunities to address socially produced barriers to care." (Card 2021, p. 8)[4]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **LGBTQ+: MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MSM**: Men who have sex with men, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **SGMSM**: sexual and gender minority men who have sex with men, **StUD**: Stimulant use disorder, **TGNB**: Transgender and non-binary
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Substance use	N/A	Meta-analysis: Pantalone 2020[5] (Supplemental)	Interventions co-targeting mental health, alcohol, and/or drug use, as well as sexual risk behavior had a **small, positive, significant effect on reducing substance use** (13 studies, d=0.17 [0.05, 0.30], p=0.008). Mixed population of participants with one or more mental health, alcohol, or drug problem. Drug use • Morgenstern 2009 (n=150 club drugs [60% StUD], MI vs Control) club drug use (d=0.61 [0.11, 1.12], p=0.018); Shoptaw 2008 (n=128 AUD/**StUD**, GCBT vs GSST) amphetamine use (d=0.5 [0.1, 0.9], p=0.015); Landovitz 2015 (n=140 **MA**, CM vs NCR) MA use (d=0.36 [0.03, 0.7], p=0.034); Parsons 2014 (n=143 drug use [68% cocaine, 17% MA], MI vs Control) NSD in drug use; Mansergh 2010 (n=1686 AOD, CBT vs Control) NSD in drug use before/during UA (p=0.085); Kurtz 2013 (n=515 AOD [62% stim], BI vs Control) NSD in drug dependence; Parsons 2018 (n=210 **MA** use, MI+CBT vs control) NSD in MA use Substance use • Kurtz 2013 (n=515 AOD [62% stim], BI vs Control) NSD in substance use during sex Alcohol use • Pachankis 2015 (Alcohol, ESTEEM vs Control) (d=1.03 [0.5, 1.56], p<0.001); Kahler 2018 (Alcohol, MI vs Control) (d=0.33 [0.02, 0.64], p=0.038); Parsons 2007 NSD in alcohol use; Velasquez 2009 (Alcohol, TTM+MI vs Referral) NSD in alcohol use; Mansergh 2010 (n=1686 AOD, CBT vs Control) NSD in alcohol use before/during UA	Behavioral interventions for Sexual Minority Men (SMM) co-targeting mental health, alcohol and drug use, as well as sexual risk behavior, antiretroviral adherence, and healthcare engagement
Risky sexual behavior	N/A	Meta-analysis: Pantalone	Interventions co-targeting mental health, alcohol, and/or drug use, as well as sexual risk behavior had a **small, positive, significant effect on reducing sexual risk behavior** (12 studies, d=0.17	Behavioral interventions for Sexual

		2020[5] (Supplemental)	[0.02, 0.32], p=0.022). Mixed population of participants with one or more mental health, alcohol, or drug problem. Drug use • Landovitz 2015 (n=140 **MA**, CM vs NCR) NSD in UAS (p=0.51); Parsons 2014 (n=143 drug use [68% cocaine, 17% MA], MI vs Control) NSD in UAI (p=0.43) Alcohol and other drug use • Kurtz 2013 (n=515 AOD [62% stim], BI vs Control) NSD in sexual risk behavior (p=0.4); Mansergh 2010 (n=1686 AOD, CBT vs Control) NSD in UAS (p=0.25); Safren 2013 (n=201 AOD & Depression, Case management vs TAU) NSD in transmission risk behavior (p=0.57) Alcohol use • Kahler 2018 (Alcohol, MI vs Control) # days of US (d=0.37 [0.06, 0.68], p=0.02); Pachankis 2015 (Alcohol, ESTEEM vs Control) UAS (d=0.59 [0.09, 1.09], p=0.022); Velasquez 2009 (Alcohol, TTM+MI vs Referral) UAS with alcohol (d=0.59 [0.31, 0.86], p<0.001) Mental Health • Brown 2019 (Mental Health, 3-sessions vs Wait-list) NSD in UAS (p=0.2); O'Cleirigh 2019 (Mental Health, CPT+Counseling vs Control) NSD in sexual risk behaviors (p=0.11); Williams 2008 (Mental Health, S-HIM vs Control) NSD in sexual risk behavior (p=0.75); Williams 2013 (Mental Health, S-HIM vs Control) NSD in URAS (p=0.92) Out of the 13 RCTs of interventions targeting drug use and sexual risk behavior, 5 RCTs identified between-group differences in reductions in sexual risk behavior. • Carrico, Nation 2015 (n=23 **MA** use, RAP vs Control) NSD in transmission risk at 3 months; Carrico, Gomez 2015 (n=21 **MA** use, CM+ARTEMIS vs CM) NSD in transmission risk at 6 months; Kurtz 2013 (n=515 AOD [62% stim], BI vs Control) NSD in sexual risk behavior (p=0.40); Landovitz 2015 (n=140 **MA**, CM vs NCR) NSD in UAS (p=0.51); Mansergh 2010 (n=1686 AOD, CBT vs Control) NSD in UAS (p=0.25); Morgenstern 2009 (n=150 club drug use [60% StUD], MI vs Control) nsd in number of unprotected sex acts. Significant reduction in number of casual sex partners (d=0.64); Parsons 2014 (n=143 drug use [68% cocaine, 17% MA], MI vs Control) NSD in UAI (p=0.43); Parsons 2018 (n=210 **MA** use, MI+CBT vs control) NSD in UAS; Rotheram-Borus 2004 (n=175 drug use, In-person BI vs Telephone BI vs Wait-list) In-person BI significantly reduced number of unprotected sex acts compared to waitlist (p<0.01), but telephone BI did not; Safren 2013 (n=201 AOD use/Mental Health, Case management vs TAU) Intervention had a greater effect on reducing transmission risk behavior among depressed patients (OR=0.11 [0.02-0.45], p<0.01), but NSD between groups in non-depressed patients (OR=1 [0.81-1.25]); Santos 2014 (n=236 substance using MSM, Brief HIV risk behavior counseling + Control vs Control=rapid HIV testing) Intervention reduced UAI w/ MA use (RR=0.26 [0.08-0.84], p=0.02); Shoptaw 2005 (n=162 **MaUD**, CBT vs CM vs CBT+CM vs GCBT) Greater URAI reduction in GCBT compared to other	Minority Men (SMM) co-targeting mental health, alcohol and drug use, as well as sexual risk behavior, antiretroviral adherence, and healthcare engagement unprotected sex, UAS = unprotected anal sex, URAS = unprotected receptive anal sex

			groups at 1 month (p< 0.01), but NSD at later follow-ups; Shoptaw 2008 (n=128 AUD/**StUD**, GCBT vs GSST) NSD between groups Uncontrolled studies • Carrico 2014 (Study 2) (n=88 **MA**, The Stonewall Project); Esposito-Smythers 2014 (n=17 alcohol/cannabis use disorder, CBT+CM); Landovitz 2012 (n=53 **MA**, CM); Mimiaga 2012 (n=16 **stim** use, BA-RR); Reback 2017 (n=585 drug use, GUYS); Smith 2017 (n=33 alcohol/drug/mental health, Project PRIDE); Wu 2011 (n=68 **MA** use, Connect with Pride); Zule 2012 (n=31 **MA** use, MI)	
		Systematic review: Knight 2019[6] (High)	Added after survey Among the 23 studies that included measures of sexual health-related outcomes (eg, HIV risk behavior), 18 reported a statistically significant effect on one or more sexual health-related outcomes. • Carrico 2014 (n=211 **MA** Stonewall Project model) reductions in meth use over the 6-months follow-up (IRR = 0.71; 95% CI: 0.52, 0.96); Colfax 2011 (n=60 **MA** Daily oral Mirtazapine (30 mg)) decreases in sexual risk including number of male partners with whom meth was used (P = .009); Landovitz 2012 (n=53 **MA** HIV-uninfected MSM self-reporting) fewer mean episodes of CAI (P = 0.05) and number of sex partners decreased significantly (P < 0.05); Lyons 2014 (n=70 **Stimulant Use** C-TALK Intervention) declines were seen between baseline and follow-up in both meth use (P < 0.001) and CAI while using meth (P < 0.02); Menza 2010 (n=127 **MA** CM 12 weeks) CM participants were somewhat more likely to provide urine samples containing meth than control participants (RR = 1.21; 95%CI: 0.95, 1.54); Mimiaga 2012 (n=16 **MA** Project IMPACT Intervention) decrease over time in the number of crystal meth episodes in the previous 3 months (P < 0.0001); Nyamathi 2017 (n=422 **Stimulant Use** Nurse case management + CM, Standard education + CM) reductions were observed in meth use (P = 0.001); Parsons 2014 (n=143 **Drug Use** MI or content-matched education) * Young gbMSM in the MI condition were less likely to use drugs (P < 0.01) and engage in CAI (P < 0.01) than those in the education condition; Reback & Fletcher 2017 (n=585 **Substance Use** Individual or group sessions) Significant reduction in sexual risk behaviors (p < 0.001); Reback 2012 (n=62 **MA** test-messaging intervention setting) decreases in frequency of meth use (P < 0.01) and unprotected sex while on meth (P < 0.01); Reback & Shoptaw 2014 (n=257 **MA** CM, CBT, CM+CBT, G-CBT) Modified G-CBT + CM produced greater effects in reducing the number of male sexual partners (p < 0.01); Santos 2014 (n= 326 **Stimulant Use** Brief Personalized Cognitive Counseling + rapid HIV testing) No reduction in any meth use (RR = 0.72; 95% CI: 0.36,1.42); Santos 2016 (n= 30 **MA** 50 mg Naltrexone or placebo 8 weeks) naltrexone was associated with reductions in meth using days (IRR = 0.78; 95%	Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine

			CI: 0.62,0.99) and binge-drinking days (IRR = 0.72; 95% CI: 0.54, 0.97) reductions; Shoptaw 2008 (n=128 **Opioid/Benzo** GCBT, GSST, group sessions) Significant reductions in meth use and concomitant sexual risky behaviors were observed for all of the participants (P < 0.05); Shoptaw 2005 (n=162 **MA** CBT, CM, CBT+CM) CBT showed shorter retention than CM and CBT + CM (P < 0.05); Strona 2006 (n=178 **MA** PROP, urine screening) Of the urine samples collected from PROP participants, 96% were negative for meth. Significant reduction in the number of sex partners among PROP participants (P < 0.05); Wu 2011 (n=68 **MA** couple-based intervention) Reports of significantly less drug use and condomless sex; Zule 2012 (n=39 **MA** Motivational or MSM drug and alcohol counselor) Reductions in meth use (P = 0.023) and number of sex partners (P = 0.037) during the last 2 months 15 of those reported a concurrent effect on both MA and sexual health-related outcomes. • Carrico 2014 (n=211 **MA** Stonewall Project model) reductions in meth use over the 6-months follow-up (IRR = 0.71; 95% CI: 0.52, 0.96); Colfax 2011 (n=60 **MA** Daily oral Mirtazapine (30 mg)) decreases in sexual risk including number of male partners with whom meth was used (P = .009); Landovitz 2012 (n=53 **MA** HIV-uninfected MSM self-reporting) fewer mean episodes of CAI (P = 0.05) and number of sex partners decreased significantly (P < 0.05); Lyons 2014 (n=70 **Stimulant Use** C-TALK Intervention) declines were seen between baseline and follow-up in both meth use (P < 0.001) and CAI while using meth (P < 0.02); Mimiaga 2012 (n=16 **MA** Project IMPACT Intervention) decrease over time in the number of crystal meth episodes in the previous 3 months (P < 0.0001); Nyamathi 2017 (n=422 **Stimulant Use** Nurse case management + CM, Standard education + CM) reductions were observed in meth use (P = 0.001); Parsons 2014 (n=143 **Drug Use** MI or content-matched education) * Young gbMSM in the MI condition were less likely to use drugs (P < 0.01) and engage in CAI (P < 0.01) than those in the education condition; Reback & Fletcher 2017 (n=585 **Substance Use** Individual or group sessions) Significant reduction in sexual risk behaviors (p < 0.001); Reback 2012 (n=62 **MA** test-messaging intervention setting) decreases in frequency of meth use (P < 0.01) and unprotected sex while on meth (P < 0.01); Santos 2014 (n= 326 **Stimulant Use** Brief Personalized Cognitive Counseling + rapid HIV testing) No reduction in any meth use (RR = 0.72; 95% CI: 0.36,1.42); Santos2016 (n= 30 **MA** 50 mg Naltrexone or placebo 8 weeks) naltrexone was associated with reductions in meth using days (IRR = 0.78; 95% CI: 0.62,0.99) and binge-drinking days (IRR = 0.72; 95% CI: 0.54, 0.97) reductions; Shoptaw 2008 (n=128 **Opioid/Benzo** GCBT, GSST, group sessions) Significant reductions in meth use and concomitant sexual risky behaviors were observed for all of the participants (P < 0.05);	

			Shoptaw 2005 (n=162 **MA** CBT, CM, CBT+CM) CBT showed shorter retention than CM and CBT + CM (P < 0.05); Strona 2006 (n=178 **MA** PROP, urine screening) Of the urine samples collected from PROP participants, 96% were negative for meth. Significant reduction in the number of sex partners among PROP participants (P < 0.05); Wu 2011 (n=68 **MA** couple-based intervention) Reports of significantly less drug use and condomless sex	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Burgess 2018[7]	Pre-post 6 wks + aftercare Australia	**Re-Wired**: treatment and peer support program for gay men and other men who have sex with men (MSM) who use methamphetamine	MSM	modest improvements in participant psychological distress, personal well-being and stage of change and reductions in methamphetamine use post intervention	
Fletcher & Reback 2022[8]	Case-control pilot 8 wks, 3-mo follow-up Outpatient	**(1) MoodGym + TAU:** A brief, computerized depression intervention based on CBT and Interpersonal Therapy (https://moodgym.com.au) (n=39) **(2) TAU:** Getting Off, a long-running outpatient MA treatment program using G-CBT and CM for GBMSM for 8 weeks followed by 4 months of continuing care (n=703)	N=742 **MA**-using cisgender gay, bisexual, and other men who have sex with men (GBMSM). Group 2 were historical controls.	**MA use (UDT):** MoodGym + TAU participants were less likely to submit an MA-positive UDS during treatment (Adjusted Treatment Effect [ATE] = 0.72; p < 0.01) compared to prior patients who received TAU alone. **Sexual risk-taking:** greater reductions in receptive condomless anal intercourse (CAI) with non–primary partners in the past 30 days (ATE = 1.39; p < 0.05) and receptive CAI with non –primary male partners while using MA (ATE. = 1.38; p < 0.05) from baseline to 3-month follow-up compared to prior patients who received TAU alone.	CESD-R not administered to the historical controls

				Depression (CESD-R): Scores did not trend strongly downward over the eight-week intervention period.	
Kurtz 2013[9]	RCT 12-month follow-up USA Community	**(1) BI**: 4 session group psychological empowerment intervention including the interaction of drugs and sex among MSM + 1 session of individual goal achievement counseling **(2) Control**: 1 session (30–45 min) individual substance use risk assessment and risk reduction counseling using the RESPECT model	N= 515 non-monogamous MSM age 18-55 with **binge drinking or drug use** (63% stimulants) in the 30 days, multiple anal sex partners, and UAI in past 90 days. Recruited via participant referral, internet and print media	Follow-up 81.6 % completed all four assessments **Number of anal sex partners**: NSD between groups in reduction. Both groups reduced over time. **Unprotected anal intercourse (UAI)**: NSD in reduced frequency (p=0.402). Both groups reduced over time. **HIV transmission risk (UAI excluding when both partners are HIV+)**: NSD between groups in reduced frequency. Both groups reduced over time. **Substance use during sex**: NSD in reduced frequency (p=0.18). Both groups reduced over time. **Drug dependence symptoms**: NSD in reduced symptoms (p=0.64). Both groups reduced over time.	In Pantalone 2020[5] Also see EtDT Prev Edu Sex
Landovitz 2015[10]	RCT, open-label 8 wks, 6-month follow-up USA Community	**(1) CM**: 8 weeks of individual voucher-based contingency management with reset contingent on 3/week stimulant-negative UDS **(2) NCR**: Noncontingent reward yoked to CM participant (incentives not tied to abstinence) All participants provided 4-day supply of postexposure prophylaxis (PEP) with tenofovir/emtricitabine and education to take in the event of exposure to HIV and present for further	N= 140 MSM without HIV who used **stimulants** (MA, amphetamine, cocaine) in past 30 days, with an HIV+ or serostatus-unknown partner in prior 3 months recruited via community advertising (37.1% White)	**Stimulant use**: Greater reduction in CM group (d=0.36 [0.03, 0.70], p=0.034) **Stimulant abstinence** (UDT-): Higher rate in CM group at 6 months in bivariate analysis (M=8.9 vs 6.1, p=0.035) and after adjusting for sociodemographics (adjusted rate ratio=1.6 [1.1-2.2], p=0.01) **Unprotected anal intercourse**: Significant decrease in incidence at 6 months in CM group (MD=3.0, p<0.001), but not NCR group (MD=1.8). However, NSD between groups in incidence rate at 6 months in bivariate analysis (M=0.8 vs 1.4, p=0.43) or in adjusted rate (p=0.39).	In Pantalone 2020[5] Also see EtDT Prev Edu Sex

		treatment. 46 (33%) participants initiated PEP during study or follow-up period.		**No. of male sexual partners**: NSD between groups at 6 months in bivariate analysis (M=1.68 vs 1.48, p=0.60) or in in adjusted rate between groups (p=0.71). **PEP course completion**: Greater in the CM group at 6 months in bivariate analysis (71% vs 31%, p=0.03) and adjusted odds (adjusted odds ratio [AOR]=7.2 [1.1–47.9], p=0.04). **PEP medication adherence**: Higher adherence in CM group at 6 months in bivariate analysis (M=0.75 vs 0.45, p=0.05) and trend towards greater adherence in CM group in adjusted odds (AOR=4.3 [0.9–21.9], p=0.08)	
Mansergh 2010[11]	RCT 12-month follow-up	(1) **CBT**: 6 group sessions of CBT (Project MIX) (2) **Control**: 6 sessions of attention control (MSM-related content unrelated to intervention)	N= 1,686 MSM (46% HIV+, 401% white)	**Sexual risk behavior**: NSD in unprotected anal sex (p=0.25) **Drug use w/ unprotected anal sex**: Trend (d= −0.11 [−0.22, 0.01], p=0.085) **Alcohol use w/ unprotected anal sex**: NSD (p=0.599)	In Pantalone 2020[5] Also see EtDT Prev Edu Sex
Mimiaga 2018[12]	RCT	**Project IMPACT:** an HIV risk reduction and behavioral activation counseling intervention for MSM--10 weekly sessions of education for HIV risk reduction, CBT for substance use reduction, and behavioral activation to improve mood, reduce substance use, and enhance motivation to engage in HIV risk reduction behavior	N=MSM without HIV who are currently using stimulants	**Sexual risk-taking:** fewer instances of condomless anal sex without the protection of preexposure prophylaxis (PrEP), relative to a control group.	Where is this from? This citation is for a study protocol with no results.
Parsons 2018[13]	RCT	**(1) MI + CBT**: 8 sessions (1 hour each) of individual MI + CBT targeting MA	N= 210 adult MSM (33% white) with HIV who use **MA** (at least 1 day of use	**Follow-up:** NSD bw groups. Overall rate 82% at 12 months	In Pantalone 2020[5]

	12-month follow-up USA Community	use and HIV medication adherence ('ACE') **(2) Education**: 8 sessions (1 hour each) of education on HIV and club drug use	during the previous 90 days and 1 day in the last 30 days) currently taking highly-active antiretroviral therapy (HAART) with poor adherence (report missing at least 3 days of medication in the last 30 days) recruited via community advertising. Baseline information-motivation-behavioral self-efficacy (IMB, Starks et al 2017 PubMed: 28092450) profile: adherence & MA 'Change Ready', 'Adherence Ready/ MA Ambivalent', 'Global Barriers' to changing adherence & MA	**MA use** (self-report): NSD bw groups in prior 30 day use (p=0.60). Both groups reduced use over time. **Medication adherence:** NSD bw groups in prior 14 day adherence. Both groups increased adherence over time. Among those with greater barriers to change ('Global Barriers' group), MI+CBT had greater improvements in adherence compared to control (p<0.05). **Viral load:** NSD between groups (n=186) **CD4 count:** NSD between groups (n=186) **Condomless anal sex** (self-report): NSD bw groups or IMB classification in prior 30 day use at 12 months (n=187). Both groups increased use over time.	Also see EtDT Prev Edu Sex
Safren 2013[14]	RCT 12-month follow-up USA Community	**(1) Case management**: 9 individual sessions provided by a medical social worker including counseling about living with HIV and HIV TRB risk reduction, including party drug use **(2) TAU**: Standard care	N= 201 adult MSM with HIV (74.6% white) who received HIV care in a community health center and who reported HIV sexual transmission-risk behavior (TRB) in the prior 6 months. **Alcohol or drug use not an inclusion criterion.**	Follow-up rate at 12 months 86% (n=172). **HIV transmission risk behavior:** NSD bn groups in anal intercourse acts with HIV-uninfected partners or partners of unknown status within the past three months. Reduced overall over time. Among participants with baseline depression screen (n=26), greater reduction for case management compared to TAU (RR=0.22 [0.08–0.58]). NSD among participants with negative depression screen (n=170). **Drug-use impairment** (PHQ): NSD bn groups in past 3-month impairment over time in ITT (p=0.39) **Serious adverse events**: no study-related SAEs occurred	In Pantalone 2020[5] Also see EtDT Prev Edu Sex

Shoptaw 2005[15]	RCT 2 week baseline period 16 weeks 6 & 12-month follow-up USA Outpatient	(1) **CM alone**: Voucher-based CM escalation w/ reset 3 UDS/wk (n=42) (2) **CBT Matrix Model alone**: Group format (n=40) (3) **CM+CBT Matrix Model** (n=40) (4) **GCBT**: Gay-Specific CBT integrating relevant cultural aspects of MA use by gay and bisexual men with Matrix Model CBT (Rawson et al., 1995). Included skills for reducing sexual risk behaviors. Group format 3 sessions/wk (n=40)	N= 162 treatment-seeking MSM with **MaUD** (SCID-verified) (61% HIV+, 80% White). Exclusions for pre-existing medical or psychiatric conditions	Retention 80% at 6 months **Sexual risk behavior:** GCBT group had a greater reduction in unprotected receptive anal intercourse compared to the other groups at 1 month ($\chi 2$ (3) = 6.75, $p < .01$), but NSD between groups at later follow-ups. NSD between groups in number of prior 30-day sexual partners. Significant reduction at the end of treatment in all groups for both measures, which were sustained at 6- and 12-month follow-up. **Retention** 80% at 6 months **Duration of treatment**: NSD between GCBT and other conditions in mean weeks in treatment **Attendance**: % of total possible sessions (CBT alone=41%, CM alone 32%, CBT+CM=74%, G-CBT alone=56%). Incorporating CM with CBT significantly increased attendance at therapy sessions over standard CBT. **Continuous stimulant abstinence** (UDS): NSD between GCBT and other conditions during the trial or at 6- or 12-month follow-up in longest period (in weeks) of consecutive MA metabolite-negative samples **Stimulant abstinence rate** (UDS): CBT Matrix Model alone group provided significantly lower % of MA-neg urine samples during the trial compared to the other three conditions (CBT=75%, CM=83%, CM+CBT=93%, G-CBT=80%; $\chi 2$ (1) = 10.03, $p < .01$). NSD between conditions at 6- or 12-month follow-up. Across groups, significant reduction in % UDS MA+ at the end of treatment	In Pantalone 2020[5] and Colfax 2010[16] Also see EtDT Prev Edu Sex

				from baseline (48% vs 17%, McNemar's Q = 18.69, p < .0001), which was sustained at 6- and 12-month follow-ups. **Other outcomes:** NSD between groups in self-reported days MA use in previous 30, Addiction Severity Index (ASI)	
Shoptaw 2008[17]	RCT USA Outpatient	(1) **G-CBT:** Gay- specific Matrix Model CBT (n=46) (2) **GSST**: Gay social support therapy HIV group 1/wk, social support group 1/wk, peer counseling 1/wk	treatment-seeking adult (18-65) MaUD MSM		
Strona 2016[18]	USA Community	CM: Positive Reinforcement Opportunity Project	MSM who use MA		

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. https://www.aezq.de/mdb/edocs/pdf/literatur/s3-gl-methamphetamine-related-disorders-long.pdf

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Manning V, Arunogiri S, Frei M, et al. *Alcohol and Other Drug Withdrawal: Practice Guidelines*. 3rd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Resources from other Guidelines

Source	Recommendation	Comments
	Getting Off: A Behavioral Treatment Intervention for Gay and Bisexual Methamphetamine Users," manual-driven intervention authored by Cathy Reback, in collaboration with colleagues (available for download at https://www.friend scommunitycenter.org/s/Getting-Off-manual_final_3_15_19.pdf).	
SAMHSA	SAMHSA, Lesbian, Gay, Bisexual, and Transgender (LGBT) Behavioral Health Equity (https://www.samhsa.gov/behavioral-healthequity/lgbt): This webpage provides information on SAMHSA's programs related to the LGBT community and SAMHSA resources for providers and programs working with the LGBT population, as well as links to other federal initiatives that seek to expand services and improve behavioral health outcomes for these individuals.	

SAMHSA	A Provider's Introduction to Substance Abuse Treatment for Lesbian, Gay, Bisexual, and Transgender Individuals (https://store.samhsa.gov/ product/Providers-Introduction-Substance-AbuseTreatment-Lesbian-Gay-Bisexual-Transgender/ SMA12-4104): This manual assists behavioral health clinicians in providing services that are sensitive to transgender and other clients from LGBT communities.	
VAC and VAADA	Policy and Practice Recommendations: for alcohol and other drugs (AOD) Service providers supporting the Trans and Gender Diverse (TGD) community https:// vac.org.au/site/assets/uploaded/622ef9ea-vac2503-reference-guide-05-web.pdf guidelines for AoD service providers supporting Trans and Gender Diverse people	From Manning 2018 (p63)[19]
	Online training module for healthcare providers: "Building sensitivity to LGBT clients accessing alcohol and drug care" A module from the University of Melbourne for any healthcare worker who would like to increase their skills and knowledge regarding lesbian, gay, bisexual and transgender clients in order to become more sensitive to their specific needs. https://edtech.le.unimelb.edu.au/login/lgbt/	From Grigg 2018 (p80)[20]

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Interventions focused on mental health, alcohol, and/or drug use, as well as sexual risk behavior had a small, positive, significant effect on reducing substance use.	Referring sexual and gender minorities to LGBTQ+ affirming programs can increase engagement, which can help reduce substance use.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Not all sexual and gender minorities require LGBTQ+ affirming programing, which could lead to decreased access to general programming if misapplied. Could be used to discriminate against people.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	The benefits of increasing treatment engagement for LGBTQ+ patients outweigh the risks of misapplication.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
* **Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	This recommendation is expected to make tailored treatment more equitably accessible for sexual and gender minorities.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies

***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
*** Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	This recommendation requires that clinicians be capable of determining when a referral to an LGBTQ+ affirming program based on the patient's history or behavior.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Evidence suggests that referring sexual and gender minorities to LGBTQ+ programs can increase engagement. This could be misapplied, but the benefits are expected to outweigh the risks assuming clinicians are capable of determining when a referral to an LGBTQ+ affirming program should be made based on the patient's history or behavior.

Subgroup Considerations

No additional subgroup considerations noted

Implementation Considerations

- Clinicians should assess sexual practice history when sufficient rapport has been established.

References

1. Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004
2. Frost MC, Blosnich JR, Lehavot K, et al. Disparities in Documented Drug Use Disorders Between Transgender and Cisgender U.S. Veterans Health Administration Patients. *J Addict Med*. 2021;15(4):334-340. doi:10.1097/ADM.0000000000000769
3. Hughto JMW, Quinn EK, Dunbar MS, Rose AJ, Shireman TI, Jasuja GK. Prevalence and Co-occurrence of Alcohol, Nicotine, and Other Substance Use Disorder Diagnoses Among US Transgender and Cisgender Adults. *JAMA Netw Open*. 2021;4(2):e2036512-e2036512. doi:10.1001/jamanetworkopen.2020.36512

4. Card K, McGuire M, Bond-Gorr J, et al. Perceived difficulty of getting help to reduce or abstain from substances among sexual and gender minority men who have sex with men (SGMSM) and use methamphetamine during the early period of the COVID-19 pandemic. *Subst Abuse Treat Prev Policy*. 2021;16(1):88. doi:10.1186/s13011-021-00425-3
5. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
6. Knight R, Karamouzian M, Carson A, et al. Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine: A systematic review. *Drug Alcohol Depend*. 2019;194:410-429. doi:10.1016/j.drugalcdep.2018.09.023
7. Burgess K, Parkhill G, Wiggins J, Ruth S, Stoovè M. Re-Wired: treatment and peer support for men who have sex with men who use methamphetamine. *Sex Health*. 2018;15(2):157. doi:10.1071/SH17148
8. Fletcher JB, Reback CJ. Optimizing outpatient treatment outcomes among methamphetamine-using gay and bisexual men through a computerized depression intervention. *J Subst Abuse Treat*. 2022;136:108663. doi:10.1016/j.jsat.2021.108663
9. Kurtz SP, Stall RD, Buttram ME, Surratt HL, Chen M. A randomized trial of a behavioral intervention for high risk substance-using MSM. *AIDS Behav*. 2013;17(9):2914-2926. doi:10.1007/s10461-013-0531-z
10. Landovitz RJ, Fletcher JB, Shoptaw S, Reback CJ. Contingency Management Facilitates the Use of Postexposure Prophylaxis Among Stimulant-Using Men Who Have Sex With Men. *Open Forum Infect Dis*. 2015;2(1). doi:10.1093/ofid/ofu114
11. Mansergh G, Koblin BA, McKirnan DJ, et al. An Intervention to Reduce HIV Risk Behavior of Substance-Using Men Who Have Sex with Men: A Two-Group Randomized Trial with a Nonrandomized Third Group. Kalichman SC, ed. *PLoS Med*. 2010;7(8):e1000329. doi:10.1371/journal.pmed.1000329
12. Mimiaga MJ, Pantalone DW, Biello KB, et al. A randomized controlled efficacy trial of behavioral activation for concurrent stimulant use and sexual risk for HIV acquisition among MSM: project IMPACT study protocol. *BMC Public Health*. 2018;18(1):914. doi:10.1186/s12889-018-5856-0
13. Parsons JT, John SA, Millar BM, Starks TJ. Testing the efficacy of combined Motivational Interviewing and Cognitive Behavioral Skills Training to reduce methamphetamine use and improve HIV medication adherence among HIV-positive gay and bisexual men. *AIDS Behav*. 2018;22(8):2674-2686. doi:10.1007/s10461-018-2086-5
14. Safren SA, O'Cleirigh CM, Skeer M, Elsesser SA, Mayer KH. Project enhance: a randomized controlled trial of an individualized HIV prevention intervention for HIV-infected men who have sex with men conducted in a primary care setting. *Health Psychol Off J Div Health Psychol Am Psychol Assoc*. 2013;32(2):171-179. doi:10.1037/a0028581
15. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134. doi:10/bkdpqf
16. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *The Lancet*. 2010;376(9739):458-474. doi:10.1016/S0140-6736(10)60753-2
17. Shoptaw S, Reback CJ, Larkins S, et al. Outcomes using two tailored behavioral treatments for substance abuse in urban gay and bisexual men. *J Subst Abuse Treat*. 2008;35(3):285-293. doi:10.1016/j.jsat.2007.11.004
18. Strona FV, McCright J, Hjord H, et al. The acceptability and feasibility of the Positive Reinforcement Opportunity Project, a community-based contingency management methamphetamine treatment program for gay and bisexual men in San Francisco. *J Psychoactive Drugs*. 2006;Suppl 3:377-383. doi:10.1080/02791072.2006.10400601
19. Manning V, Arunogiri S, Frei M, et al. *Alcohol and Other Drug Withdrawal: Practice Guidelines*. 3rd ed. Turning Point; 2018.
20. Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Stimulant Intoxication and Withdrawal

Managing Stimulant Intoxication and Withdrawal

Table 36. Agitation Medication

Recommendation: Clinicians can consider treating stimulant-induced agitation or confusion with a medication.

a. Benzodiazepines can be considered a first line treatment for managing stimulant-induced agitation and/or confusion.

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate interventions for the treatment of agitation in patients experiencing stimulant intoxication? 2. What contextual factors and implementation strategies may influence the effects of the intervention for agitation?
Population	Patients experiencing cocaine or amphetamine-type stimulant toxicity with symptoms of agitation not fully controlled by verbal and nonverbal de-escalation strategies
Intervention	Benzodiazepines
Comparison	No medication, Antipsychotics, Dexmedetomidine, Ketamine, propofol, and "ketofol"
Main Outcomes	Reduction/control of agitation weighted against side effects and adverse events
Setting	Any clinical setting where a clinician might encounter a patient experiencing stimulant intoxication
Background & Definitions	Stimulant-induced agitation and/or confusion is common especially in acute settings such as emergency departments
Abbreviations	**ARDA:** Amphetamine, related derivatives, and analogues, **N:** Number, **RoB:** Risk of Bias, **N:** Number, **RoB:** Risk of Bias, **RR:** Risk ratio, **CI:** Confidence interval, **RCT:** Randomized control trial, **SR:** Systematic review, **MA:** Meta analysis, **SoE:** Strength of evidence, , **MD:** Mean deviation, **ED:** Emergency department, **OD:** Once daily, **NMS:** Neuroleptic malignant syndrome
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Antipsychotics vs Benzodiazepines

Systematic Review and Meta-analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Adverse events	N/A	Systematic review: Connors 2019[1] (Moderate)	"There is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted" (Connors, 2019, p 1). • Conclusion based on 1 open-label RCT (Richards 1998), 19 case series and reports of antipsychotic treatment for sympathomimetic toxicity.	
Important Outcomes				
Agitation	N/A	Systematic review: Richards 2015a[2] (Moderate)	"Both drugs [antipsychotics and benzodiazepines] were effective at controlling [ARDA-associated] agitation" (p 3).	
Sedation	N/A	Systematic review: Connors 2019[1] (Moderate)	"There is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted" (Connors, 2019, p 1). Conclusions based on 1 open-label RCT (Richards 1998), 19 case series and reports of antipsychotic treatment for sympathomimetic toxicity.	Single low quality study

Characteristics of Individual studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Richards 1998[3]	Open-label RCT Emergency Department	(1) **Lorazepam** (2) **Droperidol** Both IV administered for control of agitation. Dose clinician determined, but suggested dosing by weight provided (lorazepam: <50 kg 2 mg, > 50 kg 4 mg IV; droperidol: <50 kg 2.5 mg, > 50 kg 5 mg IV)	N= 202 general agitated patients, 174 (86%) of whom used cocaine or methamphetamine	No significant difference at 5 mins, but "time interval comparison demonstrated droperidol to result in significantly greater sedation at times 10, 15, 30, and 60 min… [with] no difference in sedation profile between patients with different intoxications for both lorazepam and droperidol" (Richards, 1998, p 3).	Connors 2019[1] GRADE Level of evidence: Low

Antipsychotics

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Adverse events		Systematic review: Connors 2019[1] (Moderate)	***Cocaine toxicity:*** "In 96 subjects with cocaine toxicity treated with an antipsychotic, there were three deaths, two cardiac arrests, two seizures, and one episode of hyperthermia" (p. 1). ***Amphetamine toxicity:*** "In 330 subjects with amphetamine toxicity treated with an antipsychotic, there were two episodes of coma and QT prolongation and one episode of each: hypotension, NMS, cardiac arrest, and death" (p. 1).	
		Systematic review: Richards et al 2015b [4] (Moderate)	Out of 4 high-quality (level I) trials, 5 case series and 18 case reports of treating ARDA-related agitation and psychosis with antipsychotics, adverse events reported were two dystonic reactions (Richards, 1997; Shen, 2008), two cases of rigidity without hyperthermia concerning for mild NMS (Henderson, 2011), circulatory collapse (Koerselman and Goslinga, 1987). • "All generations of antipsychotics may result in vary varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome (NMS). Later generation atypical antipsychotics are associated with fewer extrapyramidal side effects, reflecting differences in the pharmacodynamics of limbic versus striatal dopamine-2 and serotonin 2A receptor antagonism, as well as anticholinergic properties (Haddad and Dursun, 2008). Haloperidol and ziprasidone have the highest risk of QT interval prolongation, and aripiprazole has the lowest risk (Beach et al., 2013; Chung and Chua, 2011)" (p. 3).	ATS use
		Systematic review: Richards 2016a[5] (Low)	One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).	Cocaine use
Important Outcomes				
Agitation	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	"The CNS dopaminergic receptor antagonist haloperidol and droperidol (first generation butyrophenones), ziprasidone, olanzapine, risperidone, and aripiprazole (later generation) represent the most commonly used agents for control of agitation and psychosis" (p. 3). "For control of agitation and psychosis from ARDA, butyrophenones and later-generation antipsychotics are a reasonable choice, with the understanding extrapyramidal side effects may occur" (Richards, 2015, p. 10). "A position statement from the American Association for Emergency Psychiatry recommends antipsychotics for first-line treatment of generalized agitation without an obvious reversible medical cause (Wilson et al., 2012)" (p. 10). • Conclusions based on 6 RCTs, 23 case series and reports on the use of antipsychotics to treat ARDA-associated agitation and psychosis. • RCTs include: Leelahanaj 2005 (haloperidol 5-20 mg/day 4 weeks), Sulaiman 2013 (aripiprazole 5-10 mg/day 8 weeks), Farnia 2014 (aripiprazole 15 mg or risperidone	ATS use

			4 mg/daily 6 weeks), Verachai 2014 (quetiapine 100 mg/day or haloperidol 2 mg/day 4 weeks), Richards 1997 (Droperidol <50 kg 2.5 mg, > 50 kg 5 mg IV 60 minutes), Angrist 2001 (d-amphetamine 0.5 mg/kg)	
		Systematic review: Richards et al 2016b [6] (Low)	**Antipsychotics:** "Antipsychotics may improve agitation and psychosis, but with inconsistent reduction in tachycardia and hypertension and risk of extrapyramidal adverse effects" (p. 1). • Conclusions based on 7 Level I/II studies, 3 Level III studies, and 7 Level IV/V case series and reports involving 168 subjects. • RCTs include: Lile 2008 (aripiprazole 15 mg/day 10 days), Lile 2011 (aripiprazole 15 mg/day 10 days), Richards 1998 (droperidol 5 mg 60 minutes), Sherer 1989 (8 mg haloperidol 2 days), Stoops 2007 (10 mg aripiprazole), Walsh 1994 (40 mg fluoxetine/day 4 days), Winther 2000 (250 mg lamotrigine/session in six sessions).	Cocaine use
Extrapyramidal symptoms	N/A	Meta-analysis: Shoptaw et al 2009a[7] (Not assessed)	***Olanzapine, haloperidol:*** Olanzapine 5-20 mg/day showed better improvements in extrapyramidal symptoms than haloperidol over 4 weeks in 1 RCT of 58 patients with amphetamine-induced psychosis (Leelahanaj, 2005).	ATS use Single RCT
Extrapyramidal adverse effects	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	amphetamine-type stimulant toxicity, "there were 287 patients receiving antipsychotics and 15 adverse extrapyramidal identified in this review" (pg 10).	ATS use
		Systematic review: Richards et al 2016b [6] (Low)	cocaine toxicity, there is "risk of extrapyramidal adverse effects" (p. 1).	Cocaine use

Benzodiazepines

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Adverse events	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	**Benzodiazepines:** Out of 1 high-quality (level I) trial, 6 case series and 12 case reports on use of benzodiazepines to treat ARDA-associated agitation and psychosis, • "three adverse outcomes with benzodiazepine use were reported. All were associated with failure to achieve adequate sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (Caldicott et al.,2003; Kiely et al., 2009; Lusthof et al., 2011)" (p. 3). • No incidence of over-sedation with respiratory depression or paradoxical agitation	

		Systematic review: Richards et al 2016b [6] (Low)	**Benzodiazepines:** Out of 33 studies (234 participants) of benzodiazepines and other GABA-active agents, "benzodiazepines appear to be safe." "There was one adverse event in a case report in which cardiopulmonary arrest occurred during lorazepam administration"	
Important Outcomes				
Agitation	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	**Benzodiazepines:** "One high quality study… 6 case series and 12 case reports of successful use of benzodiazepines for control of agitation but not psychosis" (p. 3). "The prehospital use of benzodiazepines has been recommended by consensus in a prior review of methylphenidate toxicity (Scharmanet al., 2007)" (p. 10).	
Sedation	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	**Benzodiazepines:** "under-sedation occurred in 3 cases identified in this review" (p. 10). • Included one RCT (Richards, 1997) of 146 ED patients with methamphetamine toxicity randomized to intravenous (IV) lorazepam vs droperidol for control of agitation. "Droperidol resulted in faster time to sedation and lorazepam required repeat dosing to achieve sedation" (Richards, 2015, p 3). "Conclude droperidol superior to lorazepam for prolonged sedation ($P < 0.05$)" (Richards, 2015, p 4). Dose clinician determined, but suggested dosing by weight provided (lorazepam: <50 kg 2 mg, > 50 kg 4 mg IV; droperidol: <50 kg 2.5 mg, > 50 kg 5 mg IV).	Single RCT

Dexmedetomidine

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Adverse events	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	"Dexmedetomidine has been … used to control agitation in adult and pediatric patients with toxicity from ARDA with no adverse effects. (p. 8). • Based on one case series and two case reports, (Akingbola and Singh, 2012; Bagdure et al., 2013; Tobias, 2010)" (p. 8).	
Important Outcomes				
Agitation	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	"Dexmedetomidine has been successfully used to control agitation in adult and pediatric patients with toxicity from ARDA" (p. 8). • Based on one case series and two case reports, (Akingbola and Singh, 2012; Bagdure et al., 2013; Tobias, 2010)	

Ketamine, propofol, and "ketofol"

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Agitation	N/A	Systematic review: Richards et al 2015b [4] (Moderate)	trials or case reports of ketamine or propofol for treatment of ARDA-induced agitation and psychosis (p. 8). "As far as other sedatives to control ARDA-induced agitation and psychosis, further studies are needed to determine the efficacy of dexmedetomidine, ketamine, propofol, and "ketofol" for this indication" (p. 10).	

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Very effective for agitation	Route of administration and specific BZD will be a factor in speed of onset of effects. Midazolam has the fastest onset of effects IM. Lorazepam onset 1-3 mins IV, 15-30 mins IM.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Very safe, few adverse effects		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison

		☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on framing: High value as an antidote or treatment for a symptom, but uncertainty when framed as chemical restraint or sedation.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Use of chemical restraint may be racially biased; however, this is probably less of a concern for BZDS compared to agents like ketamine or antipsychotics as they are less associated with use as chemical sedation and control of psychiatric disorders.	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Widely available IM and oral. Some IV shortages, but alternatives agents can be used.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Benzodiazepines are very effective for treatment of stimulant-induced agitation and are considered a first-line treatment for this purpose

Subgroup Considerations

Use of chemical restraint may be more common in minoritized populations especially based on race; however, this is probably less of a concern for BZDS compared to agents like ketamine or antipsychotics as they are less associated with use as chemical sedation and control of psychiatric disorders.

Implementation Considerations

- If medications are used, clinicians should monitor patients for medication side effects according to standard care.
    - Patients treated with benzodiazepines should be monitored for side effects such as sedation, confusion, delirium, and other known side effects of benzodiazepines.
- If the case of medication shortages, phenobarbital can be used as an alternative to parenteral BZDs.

References

1. Connors NJ, Alsakha A, Larocque A, Hoffman RS, Landry T, Gosselin S. Antipsychotics for the treatment of sympathomimetic toxicity: A systematic review. *Am J Emerg Med*. 2019;37(10):1880-1890. doi:10.1016/j.ajem.2019.01.001
2. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10/f69r7s
3. Richards JR, Derlet R, Duncan DR. Chemical restraint for the agitated patient in the emergency department: lorazepam versus droperidol. *J Emerg Med*. 1998;16(4):567-573. doi:10.1016/S0736-4679(98)00045-6
4. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10.1016/j.drugalcdep.2015.01.040
5. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10/gfv25h
6. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090
7. Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online January 21, 2009. doi:10.1002/14651858.CD003026.pub3

Table 37. Psychosis Medication

Recommendation:

1. De-escalation strategies should not delay the use of medication to manage patients who are agitated, delirious, and/or psychotic and at imminent risk for severe complications.
2. Clinicians should treat stimulant-induced psychotic symptoms with an antipsychotic medication.
    a. The urgency, formulation, and duration of antipsychotic medication treatment should be based on etiology and symptomatology.
    b. Clinicians should avoid the use of chlorpromazine and clozapine for stimulant induced psychosis as these medications may place patients at increased risk for seizure.

Clinical Question Summary

Clinical Question	1. What are the most effective and appropriate interventions for the treatment of psychosis in patients experiencing stimulant intoxication? 2. Should clinicians treat stimulant-induced psychotic symptoms with antipsychotics?
Population	Patients experiencing cocaine or amphetamine-type stimulant toxicity with symptoms of psychosis
Intervention	Antipsychotics
Comparison	Benzodiazepines, dexmedetomidine, ketamine, propofol, and other methods of psychosis management
Main Outcomes	Reduction in psychosis, side effects and adverse events
Setting	Any clinical setting where a clinician might encounter a patient experiencing stimulant intoxication
Background & Definitions	While de-escalation strategies can be effective for less severe agitation, the first course of action is usually medication in acute care settings
Abbreviations	**ARDA:** Amphetamine, related derivatives, and analogues; **BPRS:** Brief Psychiatric Rating Scale, **CGI:** Clinical Global Impression, **CI:** Confidence interval, **CNS:** Central nervous system, **MA**: Methamphetamine, **MD:** Mean difference, **N:** Number, **RoB:** Risk of Bias, **NMS:** Neuroleptic malignant syndrome, **OR:** Odds ratio, **PANSS:** The Positive and Negative Syndrome Scale, **RCT:** Randomized clinical trial, **RR:** Risk ratio, **SAPS:** Simplified Acute Physiology Score, **SMD**: Standardized Mean Difference
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Antipsychotics

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Psychotic symptoms	N/A	Meta-analysis: Srisurapanont et al 2021[1] (High)	**Author conclusion:** "This analysis suggests that olanzapine or quetiapine may be a preferred antipsychotic for [MA psychosis], although the evidence for this was rated low-quality due to the high risk of bias or indirectness/intransitivity." (p. 1) Network meta-analysis comparing reduction in overall psychotic symptoms measured with validated scales (BPRS, SAPS, PANSS) of 6 antipsychotics for MA psychosis across 6 RCTs of 389 patients. No heterogeneity (I^2 = 0 %). Visual inspection of funnel plots suggests "very low" level of publication bias. Significant differences: • **Olanzapine** > risperidone (SMD = -1.09, 95% CI -1.89 to -0.28) Quality of evidence: Low • **Quetiapine** > risperidone (SMD = -0.86, 95% CI -1.61 to -0.11) Quality of evidence: Low • Aripiprazole < **Olanzapine** (SMD = 1.36, 95% CI 0.46–2.26) Quality of evidence: Low • Aripiprazole < **Quetiapine** (SMD = 1.13, 95% CI 0.28–1.98) Quality of evidence: Low • Aripiprazole < **Haloperidol** (SMD = 0.87, 95% CI 0.14–1.60) Quality of evidence: Low • Aripiprazole < **Paliperidone extended-release** (SMD = 0.60, 95% CI 0.06–1.14) Quality of evidence: Low Included studies: • Farnia 2014 (n=53 ATS-induced, 6 wks Aripiprazole 15 mg/d vs Risperidone 4 mg/d); Leelahanaj 2005 (n=58 ATS-induced, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d); Samiei 2016 (n=44 MA-associated open-label, 3 wks Haloperidol 5-20 mg/d vs Risperidone 2-8 mg/d); Verachai 2014 (n=80 MA-induced, 4 wks Quetiapine 100-300 mg/d vs Haloperidol 2-6 mg/d); Wang 2016b (n=43 MA-associated open-label, 25 days Aripiprazole 5-15 mg/d vs Risperidone 4-6 mg/d); Wang 2020 (n=120 MA-associated, 25 days Risperidone 3-6 mg/d vs Paliperidone ER 3-9 mg/d)	ATS- or MA-associated
		Systematic review: Siefried et al 2020 [2] (High)	**Aripiprazole** > **placebo** in psychotic symptom control for MaUD with a history of psychotic symptoms in 1 RCT • Sulaiman 2013 (n=37 MaUD h/o psychosis, 8 wks aripiprazole 5-10 mg/d vs placebo)	MaUD h/o psychosis

		Systematic review: Richards et al 2015[3] (Moderate)	"For control of agitation and psychosis from ARDA, butyrophenones and later-generation antipsychotics are a reasonable choice, with the understanding extrapyramidal side effects may occur" (Richards, 2015, p. 10). • Conclusions based on 6 RCTs, 23 case series and reports on the use of antipsychotics to treat ARDA-associated agitation and psychosis. Included RCTs: • Leelahanaj 2005 (n=58 ATS psychosis 4 wks) Equivalent Olanzapine (5-20 mg/d) vs Haloperidol (5-20 mg/d); Sulaiman 2013 (n=37 MaUD h/o psychosis 8 wks) Aripiprazole (5-10 mg/d) > Placebo; Farnia 2014 (n=45 ATS 6 wks) Risperidone (4 mg/d) > Aripiprazole (15 mg); Verachai 2014 (n=80 MA 4 wks) Equivalent Quetiapine (100 mg/d) vs Haloperidol (2 mg/d); Richards 1997 (n=146 MA 60 mins) Droperidol > Lorazepam Prospective controlled • Angrist 2001 (n=18 ATS haloperidol)	ATS -associated agitation and psychosis
Dropout	N/A	Meta-analysis: Srisurapanont et al 2021[1] (High)	**No significant difference** was found; moderate heterogeneity (I^2 = 72.5 %). "Undetermined" level of publication bias based on visual inspection of the funnel plots. Network meta-analysis comparing dropout rates of 5 antipsychotics against risperidone for ATS-induced psychosis across 6 RCTs • Farnia 2014 (n=53, 6 wks Aripiprazole 15 mg/d vs Risperidone 4 mg/d); Leelahanaj 2005 (n=58, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d); Samiei 2016 (n=44 open-label, 3 wks Haloperidol 5-20 mg/d vs Risperidone 2-8 mg/d); Verachai 2014 (n=80, 4 wks Quetiapine 100-300 mg/d vs Haloperidol 2-6 mg/d); Wang 2016b (n=43 open-label, 25 days Aripiprazole 5-15 mg/d vs Risperidone 4-6 mg/d); Wang 2020 (n=120m, 25 days Risperidone 3-6 mg/d vs Paliperidone ER 3-9 mg/d)	ATS- or MA-associated
		Systematic review: Siefried et al 2020 [2] (High)	**Aripiprazole > Placebo** in retention for MaUD with a history of psychotic symptoms in 1 RCT • Sulaiman 2013 (n=37 MaUD h/o psychosis, 8 wks aripiprazole 5-10 mg/d vs placebo)	MaUD h/o psychosis
Important Outcomes				
Adverse events	N/A	Systematic review: Richards et al 2016 [4] (Low)	**3 adverse events out of 168 patients (1.8%)** treated with antipsychotics for acute cocaine toxicity**:** One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).	Acute cocaine toxicity
		Systematic review: Richards et al 2015 [3] (Moderate)	**5 adverse events out of 287 patients (1.7%)** receiving antipsychotics for ATS toxicity in the review of 4 high-quality (level I) trials, 5 case series and 18 case reports: • 2 dystonic reactions (Richards 1997; Shen 2008) • 2 cases of rigidity without hyperthermia concerning for mild NMS (Henderson, 2011) • circulatory collapse (Koerselman and Goslinga, 1987)	ATS -associated agitation and psychosis

Extrapyramidal symptoms	N/A	Meta-analysis: Shoptaw et al 2009a[5] (Not assessed)	**Olanzapine > Haloperidol** in improved extrapyramidal symptoms in 1 RCT • Leelahanaj 2005 (n=58 ATS-induced psychosis, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d)	ATS- associated
Extrapyramidal adverse effects	N/A	Systematic review: Richards et al 2015 [3] (Moderate)	**15 adverse extrapyramidal events occured in 287 patients (5.2%)** receiving antipsychotics for ATS toxicity in the review of 4 high-quality (level I) trials, 5 case series and 18 case reports.	ATS -associated agitation and psychosis
Global state	N/A	Meta-analysis: Shoptaw et al 2009a[5] (Not assessed)	**No difference** between olanzapine and haloperidol in improvements on the Clinical Global Impression (CGI) scale from baseline to endpoint in 1 RCT. Both groups improved at endpoint (paired t test, p<0.001). • Leelahanaj 2005 (n=58 ATS psychosis, 4 wks Olanzapine 5-20 mg/d vs Haloperidol 5-20 mg/d)	ATS- associated

Benzodiazepines and other GABA-active agents

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Psychotic symptoms	N/A	Systematic review: Richards et al 2015 [3] (Moderate)	1 high quality prospective randomized study (n=74), 6 case series (n=53) and 12 case reports use of benzodiazepines for control of ATS -associated agitation and psychosis (N=139) **Droperidol > Lorazepam**: • Richards et al., 1997; Prospective randomized study n=146 Methamphetamine intoxication; Summary: Droperidol superior to lorazepam for prolonged sedation ($P < 0.05$). **Lorazepam + Haloperidol + Risperidone:** • Kasick et al., 2012; Case series n=2 Mephedrone intoxication; Summary: Resolution of psychosis after lorazepam, haloperidol and risperidone. **Droperidol + Lorazepam** • Thornton et al., 2012 Case report n=1; Stimulant: MDPV Flephedrone intoxication; Summary: Resolution of psychosis with droperidol and lorazepam.	ATS -associated agitation and psychosis
Adverse events	N/A	Systematic review: Richards et al 2016 [4] (Low)	**1 adverse event out of 234 patients (0.4%)** treated with benzodiazepines for acute cocaine toxicity**:** "one adverse event in a case report in which cardiopulmonary arrest occurred during lorazepam administration"	Acute cocaine toxicity

		Systematic review: Richards et al 2015 [3] (Moderate)	**3 adverse events out of 139 patients (2.2%)** treated for ATS-associated agitation and psychosis reported in 1 high quality prospective randomized study (n=74), 6 case series (n=53) and 12 case reports. "All were associated with failure to achieve adequate sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (p. 3). • Caldicott et al., 2003 Case report p-methoxyamphetamine-related (PMA) required intubation for chemical restraint, failed sedation with midazolam • Kiely et al., 2009 Case report MA-related death from fatal ingestion, multiple doses lorazepam failed to achieve sedation • Lusthof et al., 2011 Case report Mephedrone-related extreme agitation and death, midazolam not causative Over-sedation with respiratory depression and paradoxical agitation did not occur.	ATS -associated agitation and psychosis
Treatment failures	N/A	Systematic review: Richards et al 2016 [4] (Low)	**8 treatment failures out of 234 patients (3.4%)** treated with benzodiazepines for acute cocaine toxicity	Acute cocaine toxicity
		Systematic review: Richards et al 2015 [3] (Moderate)	**3 cases of under-sedation out of 139 patients (2.2%)** • See adverse events for details	ATS -associated agitation and psychosis

Other

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Psychotic symptoms	N/A	Systematic review: Richards et al 2015 [3] (Moderate)	**Ketamine, propofol, and "ketofol":** There were no trials or case reports of ketamine or propofol for treatment of ARDA-induced agitation and psychosis" (p. 8). "As far as other sedatives to control ARDA-induced agitation and psychosis, further studies are needed to determine the efficacy of dexmedetomidine, ketamine, propofol, and "ketofol" for this indication" (p. 10).	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
2 systematic reviews have identified large reductions in symptoms with the use of antipsychotics to control ATS-associated psychosis.	Acuity and severity of symptoms should determine the agent and route of administration. For example, olanzapine is available as IM, haloperidol is available as IV and IM.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Side effects include extrapyramidal, dystonia, lowering the seizure threshold. But when dosed appropriately, they are generally infrequent (5.2% in Richards 2015).		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on framing: High value as an antidote or treatment for a symptom, but uncertainty when framed as chemical restraint or sedation.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Use of chemical restraint may be racially biased. However, good clinical guidelines, protocols, and education can reduce bias.	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Some people view use of antipsychotics and other medications a form of chemical restraint, rather than an antidote.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

There are well-developed trials demonstrating the effectiveness of antipsychotics for stimulant induced psychotic symptoms, and that the side effects associated with these medications, while significant, can be tolerated.

Subgroup Considerations

Patients with other clinical features, such as dementia with Lewy bodies, may require management with antipsychotics with less antidopaminergic effects.

Implementation Considerations

- In hospitals, antipsychotic management is generally feasible.
- In ambulatory settings…
- If medications are used, clinicians should monitor patients for medication side effects according to standard care. (Approve 80%)
    - Patients treated with antipsychotics should be monitored for side effects including extrapyramidal symptoms and for the severe adverse effects of neuroleptic malignant syndrome, hyperthermia, hypotension, orthostasis, cardiac arrest, QT prolongation, and seizures. *(Approve 80%)*
- Physical restraint should be avoided whenever possible. When used, physical restraint should be the least restrictive possible (eg, soft mitts vs wrist restraints).

Research Priorities

Future research should focus on implementation trials and longer-term outcomes for patients with stimulant-induced psychosis.

References

1. Srisurapanont M, Likhitsathian S, Suttajit S, et al. Efficacy and dropout rates of antipsychotic medications for methamphetamine psychosis: A systematic review and network meta-analysis. *Drug Alcohol Depend*. 2021;219:108467. doi:10.1016/j.drugalcdep.2020.108467
2. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs*. 2020;34(4):337-365. doi:10.1007/s40263-020-00711-x
3. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10.1016/j.drugalcdep.2015.01.040
4. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090

Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online January 21, 2009. doi:10.1002/14651858.CD003026.pub3

Table 38. Hyperadrenergic Medications

Recommendation: Clinicians should treat patients in a stimulant-induced hyperadrenergic state with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol); benzodiazepines can be considered first-line treatment for this purpose.

Clinical Question Summary

Clinical Question	What are the most effective and appropriate interventions for the treatment of hyperadrenergic symptoms that typically accompany stimulant intoxication?
Population	Patients experiencing cocaine or amphetamine-type stimulant toxicity with hyperadrenergic symptoms
Intervention	Pharmacotherapy: Antipsychotics, benzodiazepines, beta-blockers, calcium channel blockers, alpha-blockers and agonists, nitric oxide-mediated vasodilators
Comparison	Other method of symptom management
Main Outcomes	Treatment of hyperadrenergic symptoms especially tachycardia and hypertension, any adverse event, extrapyramidal adverse events
Setting	Any clinical setting
Background & Definitions	Severe hyperadrenergic symptoms can develop in the individual presenting with stimulant intoxication secondary to the rapid increase in serum catecholamines. Severe symptoms can be significant and even life-threatening due to the extreme hypertension and tachycardia that can develop if symptoms go untreated. This can be especially true for those with underlying heart conditions. Rapid identification and treatment of hyperadrenergic symptoms often result in a good prognosis. Depending on symptoms at presentation, beta blockers and other anti-hypertensives, benzodiazepines, and even antipsychotics can be beneficial in the treatment of the stimulant induced hyperadrenergic state. As cardiac complications and agitation/psychosis will be addressed elsewhere in these guidelines, the committees recommendations on management of hyperadrenergic symptoms will largely address the management of severe tachycardia and hypertension.
Abbreviations	**N:** Number, **RoB:** Risk of Bias, **SoE:** Strength of evidence, **RR:** Risk ratio, **CI:** Confidence interval, **RCT:** Randomized control trial, **ARDA:** Amphetamine, related derivatives, and analogues, **ACC:** American College of Cardiology, **AHA:** American Heart Association, **GABA:** Gamma aminobutyric acid, **CEBM:** Centre for Evidence-Based Medicine, **MAP:** Mean atrial pressure, **NMS:** Neuroleptic malignant syndrome, **HTN:** Hypertension, **BB:** Betablocker, **CCB:** Calcium channel blocker, **BZ:** Benzodiazepine, **CP:** Chest pain
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Alpha-blockers and agonists

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms	N/A	Systematic review: Richards 2015[1] Moderate	Dexmedetomidine may be effective for hyperadrenergic symptoms, but "no clinical trials specific to ARDA [Amphetamine, related derivatives, and analogues] have been published yet" (p. 10).	
Heart rate	N/A	Systematic review: Richards 2016[2] Low	Heart rate "an important component of myocardial oxygen demand" (p. 7). Alpha-adrenoceptor blocking drugs: • **Phentolamine** increased heart rate in 1 Level I study (n=29) • Doxazosin did not prevent rise in HR: 1 Level I study (n=13) • Lofexidine had no significant effect on HR, adverse effects: bradycardia, hypotension: 1 Level I study (n=11) Alpha-2-adrenoceptor agonists: Two high-quality studies, one case report. • **Dexmedetomidine** in higher dose decreased heart rate (n=53)	Cocaine cardiovascular toxicity
Hypertension	N/A	Systematic review: Richards 2016[2] Low	**Alpha-adrenoceptor blocking drugs:** • **Alpha-1 blockers** may improve hypertension "although evidence is limited" (p. 1). • "Despite limited evidence, **phentolamine** has been recommended in a previous AHA scientific statement and in some reviews as an initial treatment for persistent hypertension from cocaine" (p. 7). • **Phentolamine** resolved hypertension, tachycardia after failure by nitroglycerin and diazepam: 2 case reports • Resolution of hypertension, tachycardia with combined **phenoxybenzamine & propranolol** treatment: 1 case study • "A single case report describes successful resolution of cocaine-induced hypertensive emergency complicated by aortic dissection with **dexmedetomidine** after treatment failure with benzodiazepines, nitroglycerin, and beta-blockers.[47]" (p. 7) Dexmedetomidine resolved hypertension and tachycardia after failure of all other attempted medications. Treatments: Dexmedetomidine, labetalol, nitroglycerin, esmolol, lorazepam	Cocaine cardiovascular toxicity
		Systematic review: Richards 2015[1] Moderate	2 high-quality studies of alpha1-blockers, 1 study of alpha2-agonist for treatment of hyperadrenergic symptoms from ARDA • Alpha-blockers and clonidine "may improve hypertension (p. 10).	ATS hyperadrenergic symptoms

Tachycardia	N/A	Systematic review: Richards 2016[2] Low	**Alpha-adrenoceptor blocking drugs:** Two Level I studies, three case reports. • Alpha-1 blockers do not improve tachycardia "although evidence is limited" (p. 1). • Phentolamine resolved hypertension, tachycardia after failure by nitroglycerin and diazepam: 2 case reports • Resolution of hypertension, tachycardia with combined Phenoxybenzamine, propranolol treatment: 1 case study • "A single case report describes successful resolution of cocaine-induced hypertensive emergency complicated by aortic dissection with dexmedetomidine after treatment failure with benzodiazepines, nitroglycerin, and beta-blockers.[47]" (p. 7) Dexmedetomidine resolved hypertension and tachycardia after failure of all other attempted medications. Treatments: Dexmedetomidine, labetalol, nitroglycerin, esmolol, lorazepam	Cocaine cardiovascular toxicity
		Systematic review: Richards 2015[1] Moderate	• Alpha-1blockers do not improve tachycardia: 2 high-quality studies of alpha1-blockers • Clonidine does not improve tachycardia: 1 study of alpha2-agonists	ATS hyperadrenergic symptoms
Treatment failure	N/A	Systematic review: Richards 2016[2] Low	Dexmedetomidine No treatment failures.	Cocaine cardiovascular toxicity
Vasospasm	N/A	Systematic review: Richards 2016[2] Low	**Alpha-adrenoceptor blocking drugs:** • Alpha-1 blockers (phentolamine, doxazosin) may improve vasospasm: Two Level I studies, three case reports. • phentolamine decreased coronary vasoconstriction: 1 level I study	Cocaine cardiovascular toxicity
		Systematic review: Richards 2015[1] Moderate	• Alpha-1blockers may improve vasospasm: 2 high-quality studies of alpha1-blockers • Clonidine may improve vasospasm: 1 study of alpha2-agonists	ATS hyperadrenergic symptoms
Blood pressure	N/A	Systematic review: Richards 2016[2] Low	**Alpha-adrenoceptor blocking drugs:** • Phentolamine decreased mean arterial pressure: 1 Level I study **Alpha-2-adrenoceptor agonists** (dexmedetomidine)**:** • Dexmedetomidine in lower dose decreased mean arterial pressure: 2 Level I studies	Cocaine cardiovascular toxicity
		Systematic review: Richards 2015[1] Moderate	• Doxazosin did not prevent rise in systolic blood pressure, diastolic blood pressure: 1 Level I study (n=13) • Lofexidine No significant effect on systolic blood pressure, diastolic blood pressure; adverse effects: bradycardia, hypotension: 1 Level I study (n=11)	ATS hyperadrenergic symptoms
Other	N/A		• Dexmedetomidine decreased skin vascular resistance: 1 Level 1 study (n=11)	

Antipsychotics

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically Important Outcomes				
Dropout due to adverse events	N/A	Meta-analysis: Chan 2019a[3], Chan 2020[4]	**No difference between aripiprazole and placebo** in dropout due to adverse events in 1 high RoB RCT of in 18 patients with cooccurring cocaine and opioid dependence on methadone maintenance. • Moran 2017 (aripiprazole 15 mg/day 12 weeks)	Not intoxicated patients
		Meta-analysis: Chan 2019b[5]	**No difference between aripiprazole and placebo** in dropout due to adverse events in 2 RCTs in 143 patients with amphetamine or methamphetamine use disorder. • Coffin 2012 (aripiprazole 10 mg/day 12 weeks); Tiihonen 2007 (aripiprazole 15 mg/day 20 weeks)	Not intoxicated patients
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2016[2] Low	**Favors antipsychotic.** "Seven Level I/II studies, three Level III studies, and seven Level IV/V case series and reports involving 168 subjects have been published. Antipsychotics may improve agitation and psychosis, but with inconsistent reduction in tachycardia and hypertension and risk of extrapyramidal adverse effects" (p. 1). • RCTs: Lile (2008, aripiprazole 15 mg/day 10 days), Lile (2011, aripiprazole 15 mg/day 10 days), Richards (1998, droperidol 5 mg 60 minutes), Sherer (1989, 8 mg haloperidol 2 days), Stoops (2007, 10 mg aripiprazole), Walsh (1994, 40 mg fluoxetine/day 4 days), Winther (2000, 250 mg lamotrigine/session in six sessions).	
Dropout due to side effects	N/A	Meta-analysis: Kishi 2013[6] Not appraised	**Favors placebo compared to antipsychotic.** More dropouts due to medication side effects in antipsychotic vs placebo arms: 8 studies, n= 395, RR (95% CI) = 4.48 (1.85, 10.85), p= 0.0009. • Coffin 2012 (Aripiprazole 10 mg/day 12 weeks), Newton 2008 (Aripiprazole 15 mg OD, 2 weeks), Sulaiman 2013 (Aripiprazole 5-10 mg/day, 8 weeks), Tiihonen 2007 (Aripiprazole 15 mg/day, 20 weeks), Winhusen 2007a (Reserpine 0.5 mg/day, 12 weeks), Levin 1999 (Risperidone mean 2.1 mg/day 12 weeks), Loebl 2008 (Risperidone long-acting 25 mg IM every other week, 12 weeks), Smelson 2004 (Risperidone 1 mg/day 2 weeks). **Favors placebo compared to aripiprazole.** More dropouts due to medication side effects in aripiprazole vs placebo arms: 4 studies, n= 196, RR (95% CI) = 4.64 (1.56, 13.86), p= 0.006. • Coffin (2012) Aripiprazole 10 mg/day 12 weeks, Newton (2008) Aripiprazole 15 mg OD, 2 weeks, Sulaiman (2013, aripiprazole 5-10 mg/day 8 weeks), Tiihonen (2007) aripiprazole 15 mg/day 20 weeks. **No difference between reserpine or risperidone and placebo**. • Winhusen (2007a) Reserpine 0.5 mg/day, 12 weeks, Levin (1999) Risperidone mean 2.1 mg/day 12 weeks, Loebl (2008) Risperidone long-acting 25 mg IM every other week, 12 weeks, Smelson (2004) Risperidone 1 mg/day 2 weeks.	Not intoxicated patients. Includes studies of amphetamine, cocaine, and methamphetamine use disorder populations.

Any side effects	N/A	Meta-analysis: Indave 2016[7] Not appraised	**No difference**. Antipsychotics for cocaine use disorder, no statistically significant difference in number of participants experiencing at least one side effect: 6 RCTs, 291 participants, RR 1.01, 95% CI (0.93, 1.10). • Brown 2010 (Quetiapine 400 to 800 mg/day 12 weeks); Brown 2012 (Lamotrigine 400 mg/day 10 weeks); Hamilton 2009 (Olanzapine 20 mg/day 16 weeks); Meini 2010 (Aripriprazol 10 mg/day or ropinirole 1.5 mg x 3/day 12 weeks); Reid 2005 (Olanzapine 10 mg/day 15 days); Tapp 2015 (Quetiapine 400 mg/day 12 weeks) **No difference** in sub-analyses for lamotrigine, olanzapine or quetiapine vs placebo.	Not intoxicated patients
		Systematic review: Lee 2018[8] Moderate	**Favors placebo over aripiprazole:** For amphetamine-type stimulant use disorder, aripiprazole "may have unsafe side effects." • Coffin 2012 (10 mg/day 12 weeks), Tiihonen 2007 (15 mg/day 20 weeks). **No difference between risperidone and placebo**: Risperidone "well tolerated." • Meredith 2007 (3.6 mg/day 4 weeks), Meredith 2009 (25 mg OD 8 weeks), Solhi 2014 (2 mg OD, 3 weeks)	Not intoxicated patients
Extrapyramidal symptoms	N/A	Meta-analysis: Shoptaw 2009a[9] Not appraised	**Favors olanzapine over haloperidol:** Olanzapine 5-20 mg/day showed better improvements in extrapyramidal symptoms than haloperidol over 4 weeks in 1 RCT of 58 patients with amphetamine-induced psychosis (Leelahanaj, 2005).	
Extrapyramidal adverse effects	N/A	Systematic review: Richards 2015[1] Moderate	For amphetamine-type stimulant toxicity, "There were 287 patients receiving antipsychotics and 15 adverse extrapyramidal identified in this review" (p. 10).	
		Systematic review: Richards 2016[2] Low	For cocaine toxicity, "risk of extrapyramidal adverse effects" (p. 1). "All generations of antipsychotics may cause varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome, although later generation atypical antipsychotics are associated with fewer extrapyramidal side effects" (p. 15).	
Adverse events	N/A	Systematic review: Connors 2019[10] Moderate	**No difference between antipsychotics and benzodiazepines**. For managing cocaine or amphetamine toxicity, "there is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted" (Connors, 201, p 1). • "In 96 subjects with cocaine toxicity treated with an antipsychotic, there were three deaths, two cardiac arrests, two seizures, and one episode of hyperthermia." • "In 330 subjects with amphetamine toxicity treated with an antipsychotic, there were two episodes of coma and QT prolongation and one episode of each: hypotension, NMS, cardiac arrest, and death." • Included one open-label RCT (Richards, 1998) of 202 general agitated ED patients, 174 (86%) of whom used cocaine or methamphetamine, treated with IV lorazepam or droperidol for control of agitation. "One patient treated with droperidol developed an acute dystonic reaction, though it is not reported whether they had cocaine or amphetamine toxicity" (Connors, 2019, p 4). Dose clinician determined, but suggested dosing by weight provided (Lorazepam: <50 kg 2 mg, > 50 kg 4 mg IV; Droperidol: <50 kg 2.5 mg, > 50 kg 5 mg IV).	

		Systematic review: Richards 2015[1] Moderate	• "All generations of antipsychotics may result in vary varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome (NMS). Later generation atypical antipsychotics are associated with fewer extrapyramidal side effects, reflecting differences in the pharmacodynamics of limbic versus striatal dopamine-2 and serotonin 2A receptor antagonism, as well as anticholinergic properties (Haddad and Dursun, 2008). Haloperidol and ziprasidone have the highest risk of QT interval prolongation, and aripiprazole has the lowest risk (Beach et al., 2013; Chung and Chua, 2011)" (p. 3). • Out of 4 high-quality (level I) trials, 5 case series and 18 case reports of treating ARDA-related agitation and psychosis with antipsychotics, adverse events reported were two dystonic reactions (Richards, 1997; Shen, 2008), two cases of rigidity without hyperthermia concerning for mild NMS (Henderson, 2011), circulatory collapse (Koerselman and Goslinga, 1987).	
		Systematic review: Richards 2016[2] Low	One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).	

Benzodiazepines and other GABA-active agents

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015[1] Moderate	**Benzodiazepines:** "There were no high-quality studies of benzodiazepines for treatment of ARDA-associated hyperadrenergic state. Two level I studies of cocaine-induced chest pain compared benzodiazepines to nitroglycerin, with dual therapy having advantage over single therapy in one study (Honderick et al., 2003). In the other trial there was no difference between dual versus single agent therapy (Baumann et al., 2000). There is one case report of mephedrone toxicity with resolution of tachycardia and hypertension using lorazepam (Wood et al., 2010b)" (p. 10). "Benzodiazepines may be useful in ARDA-precipitated chest pain alone or in combination with nitroglycerin, although this is based on cocaine studies as none exist for ARDA" (p. 10).	

		Systematic review: Richards 2016[2] Low	**Benzodiazepines and other GABA-active agents**: "There were five high-quality (CEBM Level I/II) studies, three retrospective (Level III), and 25 case series/reports (Level IV/ V) supporting the use of benzodiazepines and other GABA-active agents in 234 subjects with eight treatment failures. Benzodiazepines may not always effectively mitigate tachycardia, hypertension, and vasospasm from cocaine toxicity" (p. 1). "The eight treatment failures were case reports with failure to attenuate hypertension and tachycardia" (p. 3). "Benzodiazepines are classified as Class I-B in a 2008 AHA scientific statement on cocaine-associated chest pain and myocardial infarction, and Class IIa-C in the most recent ACC/AHA guideline for the management of non-ST-elevation acute coronary syndrome" (p. 3).	
Adverse events	N/A	Systematic review: Richards 2015[1] Moderate	**Benzodiazepines:** "There is a theoretical disadvantage of benzodiazepine use for this indication secondary to intrinsic positive inotropic effects which are not widely known (Starcevic and Sicaja, 2007)" (p. 10). "Over-sedation and respiratory depression are a risk of large and repeated doses of benzodiazepines (Forster et al., 1980). Paradoxical agitation is another potential adverse effect (Short et al., 1987)" (p. 3). Out of 1 high-quality (level I) trial, 6 case series and 12 case reports on use of benzodiazepines to treat ARDA-associated agitation and psychosis, "three adverse outcomes with benzodiazepine use were reported. All were associated with failure to achieve adequate sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (Caldicott et al.,2003; Kiely et al., 2009; Lusthof et al., 2011)" (p. 3). "The adverse effects of over-sedation with respiratory depression and paradoxical agitation were not encountered" (p. 10).	
		Systematic review: Richards 2016[2] Low	**Benzodiazepines or other GABA-active agents**: Out of 33 studies (234 participants) of benzodiazepines and other GABA-active agents, "benzodiazepines appear to be safe." "There was one adverse event in a case report in which cardiopulmonary arrest occurred during lorazepam administration."	

Beta-blockers

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015[1] Moderate	**Beta-blockers:** "There were 14 high-quality (levels I, II) human studies" (p. 8). "For the ARDA-induced hyperadrenergic state, treatment with beta-blockers is a reasonable choice" (p. 10).	

		Systematic review: Richards 2016[2] Low	**Beta-blockers and b/a blockers:** "There were nine Level I/II, seven Level III, and 34 Level IV/V studies of b-blockers, with 1744 subjects, seven adverse drug events, and three treatment failures. No adverse events were reported for use of combined b/a-blockers such as labetalol and carvedilol, which were effective in attenuating both hypertension and tachycardia" (p. 1). "The use of labetalol for treatment of cocaine-associated chest pain is designated Class IIb-C in the 2013 ACC/AHA guideline focused update for the management of non-ST-elevation acute coronary syndrome" (p. 14).	
Adverse events	N/A	Systematic review: Richards 2015[1] Moderate	**Beta-blockers:** "There were 9 high-quality clinical studies, 10 case series/reports, with 227 total subjects involving the use of beta-blockers with concomitant ARDA, and one putative case of "unopposed alpha-stimulation." This proportion loosely suggests an incidence rate of only 0.4%. If, however, there is a theoretical or real risk of "unopposed –-stimulation" in the setting of toxicity from ARDA, then treatment with the combined -and ————————————————-blockers labetalol or carvedilol is a logical choice. The use of labetalol for treatment of cocaine- and methamphetamine-associated chest pain has been included by the ACCF/AHA in their most recent2012 guidelines (Supplement 34) as Class IIb-C (Anderson et al.,2013)" (p. 10). "Two case reports were identified in which beta-blockers in the presence of ARDA were implicated in acute coronary vasoconstriction. Detailed analysis of these cases show otherwise" (p. 9).	
		Systematic review: Richards 2016[2] Low	**Beta-blockers:** "Of the 1744 total patients identified in this systematic review, only seven adverse events were from putative cases of ''unopposed a-stimulation'' due to the b1/b2-blocker propranolol (n=3), and b1-blockers esmolol (n=3), and metoprolol (n=1). No cases were attributed to the use of mixed b1/b2/a1-blockers" (p. 15). "No adverse events were reported for use of combined b/a-blockers such as labetalol and carvedilol" (p. 1).	

Calcium channel blockers

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015[1] Moderate	**Calcium channel blockers:** Three level II evidence studies, one case series, three case reports on the use of calcium channel blockers for toxicity from ARDA. "Calcium channel blockers are a reasonable choice to treat ARDA-induced hypertension, but not necessarily tachycardia. However the number of studies is small. The dihydropyridine-class calcium channel blockers such as nifedipine and amlodipine are more likely to result in reflex tachycardia compared to the benzothiazepine-and phenylalkylamine-class agents such as diltiazem and verapamil (Olson, 2013). The current ACCF/AHA guidelines include recommendations for IV or oral calcium channel blockers as Class I-C in the setting of chest pain with ST-segment changes, and Class IIa-C for chest pain without ST-segment changes" (p. 10).	

		Systematic review: Richards 2016[2] Low	**Calcium channel blockers:** "There were seven Level I/II, one Level III, and seven Level IV/V studies involving 107 subjects and one treatment failure. Calcium channel blockers may decrease hypertension and coronary vasospasm, but not necessarily tachycardia" (p. 1). "The 2013 ACC/AHA guideline focused update on the management of non-ST-elevation acute coronary syndrome includes recommendations for oral or IV calcium channel blockers as Class I-C in the setting of cocaine-induced chest pain with ST-segment changes, and Class IIa-C for chest pain without ST-segment changes.[" (p. 7).	

Nitric oxide-mediated vasodilators

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015[1] Moderate	**Nitric oxide-mediated vasodilators:** two case reports using nitroprusside and 4 case reports using nitroglycerin for ARDA-induced hyperadrenergic state. "Nitroglycerin is recommended as ACCF/AHA Class I-C for treatment of cocaine and ARDA-associated chest pain but should be given with the recognition it may result in reflex tachycardia. Nitroprusside may ameliorate peripheral arterial vasospasm and hypertension, but no clinical studies exist at present" (p. 10).	
		Systematic review: Richards 2016[2] Low	**Nitric oxide-mediated vasodilators: "**There were six Level I/II, one Level III, and 25 Level IV/V studies conducted in 246 subjects with 11 treatment failures and two adverse drug events. Nitroglycerin may lead to severe hypotension and reflex tachycardia" (p. 1). "With regard to the 11 treatment failures, nitroglycerin did not reduce blood pressure and heart rate in five case reports. There was a failure to mitigate chest pain and/or vasospasm in five case reports. Finally, there was one failure to resolve a cocaine-associated hypertensive emergency with nitroprusside" (p. 7). "Nitroglycerin is recommended as ACC/AHA Class I-C for treatment of cocaine-associated chest pain" (p. 7).	
Adverse events	N/A	Systematic review: Richards 2016[2] Low	**Nitric oxide-mediated vasodilators:** Adverse events with nitroglycerin were severe hypotension (n=2). For nitroglycerin, "potential for hypotension, reflex tachycardia, and treatment failure does exist, however, and should be recognized by the treating clinician" (p. 7).	

Existing Guidelines

Holmwood C, Gowing L. Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults. Clinical Guideline No. CG284. Drug and Alcohol Services South Australia (DASSA); 2019.

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Treatment of hyperadrenergic (tachycardia and HTN): Richards (2015)[1] moderate • BZ: low quality related to chest pain only • BB: high quality for use (14 level I, II studies) • CCB: (level II) good for HTN but not necessarily tachycardia • Alpha blocker and agnostic: (level II) blockers and clonidine useful in HTN and vasospasm but not tachycardia. Dexmedetomidine useful in agitation and hyperadrenergic symptoms but no clinical trials specific to ARDA. • Nitric oxide-mediated vasodilators: nitro for ARDA and cocaine induced CP but may cause reflex tachycardia. Nitroprusside can be helpful but no clinical trials exist. Richards (2016)[2] low • Antipsychotics: improve agitation and psychosis, but with inconsistent reduction in tachycardia and hypertension • Alpha 1 blocker: limited evidence. Useful in hypertension but not tachy • Alpha 2 agonist: dexmedetomidine at low dose treated hypertension and higher dose decreased heart rate	• CCB: The dihydropyridine-class calcium channel blockers (nifedipine and amlodipine) are more likely to result in reflex tachycardia compared to the benzothiazepine-and phenylalkylamine-class (diltiazem and verapamil) (Olson, 2013). • Alpha 1 blocker: Despite limited evidence, phentolamine has been recommended in a previous AHA scientific statement and in some reviews as an initial treatment for persistent hypertension from cocaine. Decreased MAP but increased heart rate.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Drop out: antipsychotics • Chan (2019a, 2019b and 2020)[3-5]: no difference aripiprazole vs placebo • Kishi (2013)[6] Not appraised: more dropout with aripiprazole versus placebo but not reserpine/risperidone Any adverse event • Indave (2016)[7] Not appraised: no difference in olanzepine, aripiprazole, or quetiapine for cocaine • Lee (2018)[8] Moderate: amphetamine use aripiprazole has potential severe side effects but risperidone well tolerated	Drop out: studies not in stimulant intoxicated individuals but in those with cocaine or stimulant use. Adverse Connors (2019)[10]: **Antipsychotics:** "In 96 subjects with cocaine toxicity treated with an antipsychotic, there were three deaths, two cardiac arrests, two seizures, and one episode of hyperthermia." **Antipsychotics:** "In 330 subjects with amphetamine toxicity treated with an antipsychotic, there were two episodes of	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

• Connors (2019)[10] Moderate: For managing cocaine or amphetamine toxicity, "there is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted"
• Richards (2015)[1] Moderate:
  • Antipsychotics: All generations of antipsychotics may result in vary varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome (NMS).
  • BZ: Over-sedation and respiratory depression are a risk of large and repeated doses of benzodiazepines (Forster et al., 1980). Paradoxical agitation is another potential adverse effect (Short et al., 1987)" (p. 3). Neither noted
  • **Beta-blockers:** 0.4% incidence rate (N=227) of "unopposed alpha-stimulation. Labetalol or carvedilol is a logical choice for beta blocker.
• Richards (2016)[2] Low
  • **Antipsychotics:** One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).
  • **Benzodiazepines or other GABA-active agents**: benzodiazepines appear to be safe.
  • **Beta-blockers:** "Of the 1744 total patients identified in this systematic review, only seven adverse events were from putative cases of ''unopposed a-stimulation'' due to the b1/b2-blocker propranolol (n=3), and b1-blockers esmolol (n=3), and metoprolol (n=1). No cases were attributed to the use of mixed b1/b2/a1-blockers" (p. 15). "No adverse events were reported for use of combined b/a-blockers such as labetalol and carvedilol" (p. 1).
  • **Nitric oxide-mediated vasodilators:** Adverse events with nitroglycerin were severe hypotension (n=2). For nitroglycerin, "potential for hypotension, reflex tachycardia, and treatment failure does exist
Extrapyramidal side effects
	coma and QT prolongation and one episode of each: hypotension, NMS, cardiac arrest, and death."
	
	Richards (2015)[1]:
	  • Later generation atypical antipsychotics: fewer extrapyramidal side effects (Haddad and Dursun, 2008).
	  • Haloperidol and ziprasidone have the highest risk of QT interval prolongation, and aripiprazole has the lowest risk (Beach et al., 2013; Chung and Chua, 2011)" (p. 3).
	  • The use of labetalol for treatment of cocaine- and methamphetamine-associated chest pain has been included by the ACCF/AHA in their most recent2012 guidelines (Supplement 34) as Class IIb-C (Anderson et al.,2013)" (p. 10).	

• Shoptaw (2009a)[9] Not appraised: olanzepine better profile than haloperidol • Richards (2015)[1] Moderate: 15/287 with extrapyramidal • Richards (2016)[2] Low: All generations of antipsychotics may cause varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome, although later generation atypical antipsychotics are associated with fewer extrapyramidal side effects"		
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
*** Values and preferences:** Confidence and variability in values and preferences of stakeholders. Is there important variability in how much people value the main outcomes? Is there uncertainty about how much people value the main outcomes?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes

		☐ Yes
***Equity:** What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability:** Is the option acceptable to key stakeholders (patients, caregivers, providers)?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

When assessing stimulant intoxication, clinicians should assess hyperadrenergic signs and symptoms, including tachycardia, hypertension, hyperthermia, and agitation. Ongoing monitoring and management of vital signs—especially heart rate and blood pressure—is critical to prevent complications that may result from untreated sympathomimetic toxicity. GABAergic agents are the primary treatment for stimulant-related hyperadrenergic symptoms. Significant hyperadrenergic symptoms should typically be managed in an acute care setting.

Subgroup Considerations

None noted

Implementation Considerations

- If medications are used, clinicians should monitor patients for medication side effects according to standard care. (Approve 80%)
    - Patients treated with benzodiazepines should be monitored for side effects such as sedation, confusion, delirium, and other known side effects of benzodiazepines. *(Approve 80%)*
    - Patients treated with antipsychotics should be monitored for side effects including extrapyramidal symptoms and for the severe adverse effects of neuroleptic malignant syndrome, hyperthermia, hypotension, orthostasis, cardiac arrest, QT prolongation, and seizures. *(Approve 80%)*

References

1. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: A systematic clinical review. *Drug Alcohol Depend.* 2015;150:1-13. https://doi.org/10/f69r7s
2. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol (Phila)*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090
3. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-analysis. *J Gen Intern Med*. 2019;34(12):2858-2873. doi:10.1007/s11606-019-05074-8
4. Chan B, Freeman M, Ayers C, et al. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. *Drug Alcohol Depend*. 2020;216:108193. doi:10.1016/j.drugalcdep.2020.108193
5. Chan B, Freeman M, Kondo K, et al. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. *Addiction*. 2019;114(12):2122-2136. doi:10.1111/add.14755
6. Kishi T, Matsuda Y, Iwata N, Correll CU. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2013;74(12):e1169-1180. doi:10.4088/JCP.13r08525
7. Indave BI, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. *Cochrane Database Syst Rev*. 2016. https://doi.org/10/f8gwnx
8. Lee N, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend.* 2018;191:309-337. https://doi.org/10/gfw5px
9. Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. *Cochrane Database Syst Rev*. 2009. https://doi.org/10/dg2tpm
10. Connors NJ, Alsakha A, Larocque A, Hoffman RS, Landry T, Gosselin S. Antipsychotics for the treatment of sympathomimetic toxicity: A systematic review. *Am J Emerg Med*. 2019;37(10):1880-1890. doi:10.1016/j.ajem.2019.01.001

Table 39. Hyperadrenergic Adjunct

Recommendation: If the hyperadrenergic state persists despite appropriate improvement in agitation and neuromuscular hyperactivity following treatment with benzodiazepines or other GABAergic agent, clinicians can consider adjunctive treatment with the following medications:

a. A beta-blocker with concomitant alpha-1 antagonism (eg, carvedilol, labetalol)
b. An alpha-2 adrenergic agonist (eg, clonidine for mild to moderate symptoms, dexmedetomidine for severe symptoms)
c. Where beta blockers are contraindicated, clinicians can consider other pharmaceutical options such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, with consideration of other clinically relevant signs and symptoms.
d. While calcium channel blockers alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators may be most beneficial in treating hypertension or vasospasm, clinicians should be alert to potential side effects, including poor control over tachycardia or reflex tachycardia.

Clinical Question Summary

Clinical Question	What adjunctive treatments can be considered for managing hyperadrenergic symptoms that typically accompany stimulant intoxication?
Population	Patients experiencing cocaine or amphetamine-type stimulant toxicity with hyperadrenergic symptoms
Intervention	Pharmacotherapy: Antipsychotics, benzodiazepines, beta-blockers, calcium channel blockers, alpha-blockers and agonists, nitric oxide-mediated vasodilators
Comparison	Other method of symptom management
Main Outcomes	Treatment of hyperadrenergic symptoms especially tachycardia and hypertension, any adverse event, extrapyramidal adverse events
Setting	Any clinical setting
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

See Hyperadrenergic Medications

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Alpha-blocker agonists (clonidine, dex) Richards (2015)[1] Precedex better supported Richards (2016)[2] **Beta-blockers** Richards (2015)[1] Richards (2016)[2] Supported, preference for non-selective/combination **Calcium channel blockers** Better for hypertension not tachycardia **Nitric-oxide mediated vasodialators** Can be considered, but better support for use in chest pain Maybe nitroprusside	Beta-blockers preference for non-selective/combination Standard treatment for hyperadrenergic	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Medication side effects – overcompensation, reflex symptoms. **Calcium channel blockers** Potential for reflex tachycardia with dihydroperidine class, although they are preferred in some situations, eg, coronary vasoconstriction, HTN emergency w/ reflex bradycardia. **Nitric-oxide mediated vasodilators** Potential for reflex tachycardia and severe hypotension	Depends on medication - Small to moderate. **Calcium channel blockers** Dihydroperidine class less preferred to benzothiazepine- and phenylalkylamine-class agents such as diltiazem and verapamil	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies

***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Beta blockers are generally contraindicated in patients with cocaine intoxication and cardiovascular disease[240]; this is an area of ongoing controversy in the field. Many experts recommend alternative medications such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, as symptoms indicate, to achieve similar effects in patients with stimulant intoxication.
Benefits of managing persistent hyper states outweigh side effect profiles of medications used.

Subgroup Considerations

It is important to consider that these pharmaceutical classes may be most beneficial in treating hypertension and vasospasm but may result in poor control of reflex tachycardia. Implementation Considerations

Implementation Considerations

Clinicians should monitor for medication side effects with usual care.

References

1. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: A systematic clinical review. *Drug Alcohol Depend.* 2015;150:1-13. https://doi.org/10/f69r7s
2. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol (Phila)*. 2016;54(5):345-364. doi:10.3109/15563650.2016.1142090

Table 40. Hypertensive Emergency

Recommendation: If a patient with stimulant intoxication is experiencing a hypertensive emergency, clinicians should:

a. use short-acting agents such as sodium nitroprusside, phentolamine, or dihydropyridine-type calcium channel blockers;
b. avoid long-acting antihypertensives to avoid abrupt hemodynamic collapse; and
c. use nitroglycerin if the patients exhibits signs or symptoms of cardiac ischemia.

Clinical Question Summary

Clinical Question	What are effective interventions for hypertensive emergency accompanying stimulant intoxication?
Population	Patients with stimulant intoxication experiencing a hypertensive emergency
Intervention	Interventions for hypertensive emergency
Main Outcomes	Resolved hypertensive emergency
Setting	Acute care settings
Background & Definitions	Hypertensive emergency is an acute and significant elevation in blood pressure and can be associated with signs of organ damage
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Resolution of HTN emergency	N/A	Systematic review: Richards 2016[1] (Low)	Case reports of cocaine-associated hypertensive emergency: • **Dexmedetomidine** resolved hypertensive emergency complicated by aortic dissection after failure of Lorazepam, nitroglycerin, esmolol, labetalol (AEs=0) (Javed Case Rep Med 2011) • **Nitroprusside** failed to resolve hypertensive emergency, rescue with **captopril** (AEs=0) (Grewal & Miller Acta Neurol 1991;13:279-281)	
		Systematic review: Richards 2015[2] (Moderate)	Case series of successful treatment of ATS-associated hypertensive emergency from: • Ephedrine and pseudoephedrine using **propranolol** (n=2) (Burkhart JAMA 1992;249:1477-1479) Case reports of successful treatment of ATS-associated hypertensive emergency from:	

			• Ephedrine using **nitroprusside** (Zahn J Emerg Med 1999;17:289-291) • Ephedrine and pseudoephedrine using **nifedipine** (Heyman, DICM 1991;25:1068-1070) • Pseudoephedrine with **Labetalol** (Mariani Am J Emerg Med 1986;4:141-142) • Phenylpropanolamine using **Phentolamine** (Duvernoy N Engl J Med 1969;280:877)	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Case reports show successful management of hypertensive emergency in those using stimulants with nitroprusside, labetolol, phentolamine and nifedipine		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No reported undesirable effects. Consider side effect profile of medication and complications	Avoid long acting antihypertensives as they may cause abrupt hemodynamic collapse in patients who have been using stimulants and may have depleted stores of norepinephrine.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Risks of untreated hypertensive emergency are greater than risk of medication side effects		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☐ No ☐ Varies

***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Case reports show successful management of hypertensive emergency in those using stimulants with nitroprusside, labetolol, phentolamine and nifedipine.

Subgroup Considerations

None noted

Implementation Considerations

References

1. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol (Phila)*. 2016;54(5):345-364. doi:10/gfv25h
2. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10/f69r7s

Table 41. Chest Pain Medication

Recommendation: For patients experiencing chest pain during stimulant intoxication, clinicians should initiate treatment for the underlying intoxication with GABAergic agents (eg, benzodiazepines, phenobarbital, propofol) as long as there are no clinical contraindications.

Clinical Question Summary

Clinical Question	What are the most effective and appropriate interventions for the treatment of chest pain in patients experiencing stimulant intoxication?
Population	Patients experiencing cocaine or amphetamine-type stimulant toxicity with chest pain
Intervention	Pharmacotherapy: Antipsychotics, benzodiazepines, beta-blockers, calcium channel blockers, alpha-blockers and agonists, nitric oxide-mediated vasodilators
Comparison	Other method of symptom management
Main Outcomes	Treatment of chest pain, any adverse event, extrapyramidal adverse events
Setting	Hospital/Emergency Department or other high acuity clinical setting
Background & Definitions	Notes: • Chest pain is a sign of acute methamphetamine intoxication (Braunwarth 2016) • "The most common presenting complaint of patients in emergency departments who have consumed cocaine is chest pain [7], while methamphetamine-related chest pain is relatively less common with only 4.5% of patients in one series of amphetamine users presented with chest pain [27]." (Duflou, 2020, p. 177) • "Cocaine is considered a cardiovascular risk factor for developing acute coronary syndrome (ACS), yet it is not included in the frequently used GRACE (The Global Registry of Acute Coronary Events), TIMI (The thrombolysis in myocardial infarction) and HEART (History, ECG, Age, Risk factors en Troponin) risk stratification scores. Moreover, many guidelines provide limited or no advice on how to diagnose and treat cocaine-associated chest pain (CACP), although 6% of these patients develop cocaine-induced myocardial infarction (CIMI) [2–5]." (Gresnigt et al., 2021, p. 23) • "In 2008, the American Heart Association (AHA) issued a scientific statement on the management of CACP and CIMI, which states that in 40 % of all cocaine associated emergency department visits, patients present with chestpain. [6] Multiple studies showed that approximately 6% of these patients develop CIMI [7,8]. The incidence of CIMI among all young patients (18–45 years) with myocardial infarction is about 25 %, and their prognosis is worse [9]." (Gresnigt et al., 2021, p. 23)
Abbreviations	**N:** Number, **RoB:** Risk of Bias, **MA:** Methamphetamine, **SoE:** Strength of evidence, **RR:** Risk ratio, **CI:** Confidence interval, **RCT:** Randomized control trial, **ARDA:** Amphetamine, related derivatives, and analogues, **ACC:** American College of Cardiology, **AHA:** American Heart Association, **GABA:** Gamma aminobutyric acid, **CEBM:** Centre for Evidence-Based Medicine, **MAP:** Mean atrial pressure, **NMS:** Neuroleptic malignant syndrome, **HTN:** Hypertension, **BB:** Betablocker, **CCB:** Calcium channel blocker, **BZ:** Benzodiazepine, **CP:** Chest pain
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Alpha-blockers and agonists

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2016[1] Low	**Alpha-adrenoceptor blocking drugs:** Two Level I studies, three case reports. • Alpha-1 blockers may improve hypertension and vasospasm, but not tachycardia, although evidence is limited" (p. 1). • "Despite limited evidence, phentolamine has been recommended in a previous AHA scientific statement and in some reviews as an initial treatment for persistent hypertension from cocaine. " (p. 7). • "One Level I study showed phentolamine decreased MAP [mean arterial pressure] but increased heart rate, which is an important component of myocardial oxygen demand" (p. 7). **Alpha-2-adrenoceptor agonists** (dexmedetomidine)**:** Two high-quality studies, one case report. • Dexmedetomidine decreased MAP [mean arterial pressure], and skin vascular resistance. • Dexmedetomidine in lower dose decreased MAP [mean arterial pressure]; higher dose decreased HR [heart rate]" (p. 1). • No treatment failures.	
		Systematic review: Richards 2015 [2] Moderate	• 2 high-quality studies of alpha1-blockers, 1 study of alpha2-agonist for treatment of hyperadrenergic symptoms from ARDA • "Alpha-blockers and clonidine may improve hypertension and vasospasm but not tachycardia, and neither is included in the ACCF/AHA guidelines" (p. 10). • "Dexmedetomidine may be effective for both agitation and hyperadrenergic symptoms, but no clinical trials specific to ARDA have been published yet" (p. 10).	ARDA = Amphetamine, related derivatives, and analogues

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Antipsychotics

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Adverse events	N/A	Systematic review: Connors 2019[3] Moderate	For managing cocaine or amphetamine toxicity, "there is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted" (Connors, 201, p 1). "In 96 subjects with cocaine toxicity treated with an antipsychotic, there were three deaths, two cardiac arrests, two seizures, and one episode of hyperthermia." "In 330 subjects with amphetamine toxicity treated with an antipsychotic, there were two episodes of coma and QT prolongation and one episode of each: hypotension, NMS, cardiac arrest, and death." Included one open-label RCT (Richards, 1998) of 202 general agitated ED patients, 174 (86%) of whom used cocaine or methamphetamine, treated with IV lorazepam or droperidol for control of agitation. "One patient treated with droperidol developed an acute dystonic reaction, though it is not reported whether they had cocaine or amphetamine toxicity" (Connors, 2019, p 4). Dose clinician determined, but suggested dosing by weight provided (Lorazepam: <50 kg 2 mg, > 50 kg 4 mg IV; Droperidol: <50 kg 2.5 mg, > 50 kg 5 mg IV).	
		Systematic review: Richards 2015[2] Moderate	"All generations of antipsychotics may result in vary varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome (NMS). Later generation atypical antipsychotics are associated with fewer extrapyramidal side effects, reflecting differences in the pharmacodynamics of limbic versus striatal dopamine-2 and serotonin 2A receptor antagonism, as well as anticholinergic properties (Haddad and Dursun, 2008). Haloperidol and ziprasidone have the highest risk of QT interval prolongation, and aripiprazole has the lowest risk (Beach et al., 2013; Chung and Chua, 2011)" (p. 3). Out of 4 high-quality (level I) trials, 5 case series and 18 case reports of treating ARDA-related agitation and psychosis with antipsychotics, adverse events reported were two dystonic reactions (Richards, 1997; Shen, 2008), two cases of rigidity without hyperthermia concerning for mild NMS (Henderson, 2011), circulatory collapse (Koerselman and Goslinga, 1987).	
		Systematic review: Richards 2016[1] Low	One dystonic reaction, one cardiac arrest, and "seizure, hyperthermia, and cardiac arrest after intramuscular haloperidol was given to an agitated cocaine-toxic patient" (p. 15).	
Important Outcomes				
Hyperadrenergic symptoms	N/A	Systematic review: Richards 2016 [1] Low	"Seven Level I/II studies, three Level III studies, and seven Level IV/V case series and reports involving 168 subjects have been published. Antipsychotics may improve agitation and psychosis, but with inconsistent reduction in tachycardia and	

(hypertension, tachycardia)			hypertension and risk of extrapyramidal adverse effects" (p. 1). RCTs: Lile (2008, aripiprazole 15 mg/day 10 days), Lile (2011, aripiprazole 15 mg/day 10 days), Richards (1998, droperidol 5 mg 60 minutes), Sherer (1989, 8 mg haloperidol 2 days), Stoops (2007, 10 mg aripiprazole), Walsh (1994, 40 mg fluoxetine/day 4 days), Winther (2000, 250 mg lamotrigine/session in six sessions).	
Dropout due to side effects	N/A	Meta-analysis: Kishi 2013 [4] Not appraised	More dropouts due to medication side effects in antipsychotic vs placebo arms: 8 studies, n= 395, RR (95% CI) = 4.48 (1.85, 10.85), p= 0.0009. • Coffin 2012 (Aripiprazole 10 mg/day 12 weeks), Newton 2008 (Aripiprazole 15 mg OD, 2 weeks), Sulaiman 2013 (Aripiprazole 5-10 mg/day, 8 weeks), Tiihonen 2007 (Aripiprazole 15 mg/day, 20 weeks), Winhusen 2007a (Reserpine 0.5 mg/day, 12 weeks), Levin 1999 (Risperidone mean 2.1 mg/day 12 weeks), Loebl 2008 (Risperidone long-acting 25 mg IM every other week, 12 weeks), Smelson 2004 (Risperidone 1 mg/day 2 weeks). More dropouts due to medication side effects in aripiprazole vs placebo arms: 4 studies, n= 196, RR (95% CI) = 4.64 (1.56, 13.86), p= 0.006. • Coffin (2012) Aripiprazole 10 mg/day 12 weeks, Newton (2008) Aripiprazole 15 mg OD, 2 weeks, Sulaiman (2013, aripiprazole 5-10 mg/day 8 weeks), Tiihonen (2007) aripiprazole 15 mg/day 20 weeks. No difference for reserpine or risperidone vs placebo. • Winhusen (2007a) Reserpine 0.5 mg/day, 12 weeks, Levin (1999) Risperidone mean 2.1 mg/day 12 weeks, Loebl (2008) Risperidone long-acting 25 mg IM every other week, 12 weeks, Smelson (2004) Risperidone 1 mg/day 2 weeks.	Not intoxicated patients. Includes studies of amphetamine, cocaine, and methamphetamine use disorder populations.
Any side effects	N/A	Meta-analysis: Indave 2016 [5] Not appraised	Antipsychotics for cocaine use disorder, no statistically significant difference in number of participants experiencing at least one side effect: 6 RCTs, 291 participants, RR 1.01, 95% CI (0.93, 1.10). • Brown 2010 (Quetiapine 400 to 800 mg/day 12 weeks); Brown 2012 (Lamotrigine 400 mg/day 10 weeks); Hamilton 2009 (Olanzapine 20 mg/day 16 weeks); Meini 2010 (Aripriprazol 10 mg/day or ropinirole 1.5 mg x 3/day 12 weeks); Reid 2005 (Olanzapine 10 mg/day 15 days); Tapp 2015 (Quetiapine 400 mg/day 12 weeks) No difference in sub-analyses for lamotrigine, olanzapine or quetiapine vs placebo.	Not intoxicated patients
		Systematic review: Lee 2018[6] Moderate	For amphetamine-type stimulant use disorder, aripiprazole "may have unsafe side effects." Coffin 2012 (10 mg/day 12 weeks), Tiihonen 2007 (15 mg/day 20 weeks). Risperidone "well tolerated." Meredith 2007 (3.6 mg/day 4 weeks), Meredith 2009 (25 mg OD 8 weeks), Solhi 2014 (2 mg OD, 3 weeks)	Not intoxicated patients
Extrapyramidal symptoms	N/A	Meta-analysis: Shoptaw 2009 [7] Not appraised	Olanzapine 5-20 mg/day showed better improvements in extrapyramidal symptoms than haloperidol over 4 weeks in 1 RCT of 58 patients with amphetamine-induced psychosis (Leelahanaj, 2005).	

Extrapyramidal adverse effects	N/A	Systematic review: Richards 2015[2] Moderate	For amphetamine-type stimulant toxicity, "There were 287 patients receiving antipsychotics and 15 adverse extrapyramidal identified in this review" (p. 10).	
		Systematic review: Richards 2016 [1] Low	For cocaine toxicity, "risk of extrapyramidal adverse effects" (p. 1). "All generations of antipsychotics may cause varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome, although later generation atypical antipsychotics are associated with fewer extrapyramidal side effects" (p. 15).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Benzodiazepines and other GABA-active agents

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Adverse events	N/A	Systematic review: Richards 2015 [2] Moderate	"There is a theoretical disadvantage of benzodiazepine use for this indication secondary to intrinsic positive inotropic effects which are not widely known (Starcevic and Sicaja, 2007)" (p. 10). "Over-sedation and respiratory depression are a risk of large and repeated doses of benzodiazepines (Forster et al., 1980). Paradoxical agitation is another potential adverse effect (Short et al., 1987)" (p. 3). Out of 1 high-quality (level I) trial, 6 case series and 12 case reports on use of benzodiazepines to treat ARDA-associated agitation and psychosis, "three adverse outcomes with benzodiazepine use were reported. All were associated with failure to achieve adequate sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (Caldicott et al.,2003; Kiely et al., 2009; Lusthof et al., 2011)" (p. 3). "The adverse effects of over-sedation with respiratory depression and paradoxical agitation were not encountered" (p. 10).	
		Systematic review: Richards 2016[1] Low	Out of 33 studies (234 participants) of benzodiazepines and other GABA-active agents, "benzodiazepines appear to be safe." "There was one adverse event in a case report in which cardiopulmonary arrest occurred during lorazepam administration."	
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015 [2] Moderate	"There were no high-quality studies of benzodiazepines for treatment of ARDA-associated hyperadrenergic state. Two level I studies of cocaine-induced chest pain compared benzodiazepines to nitroglycerin, with dual therapy having advantage over single therapy in one study (Honderick et al., 2003). In the other trial there was no difference between dual versus single agent therapy (Baumann et al., 2000). There is	

			one case report of mephedrone toxicity with resolution of tachycardia and hypertension using lorazepam (Wood et al., 2010b)" (p. 10). "Benzodiazepines may be useful in ARDA-precipitated chest pain alone or in combination with nitroglycerin, although this is based on cocaine studies as none exist for ARDA" (p. 10).	
		Systematic review: Richards 2016 [1] Low	"There were five high-quality (CEBM Level I/II) studies, three retrospective (Level III), and 25 case series/reports (Level IV/ V) supporting the use of benzodiazepines and other GABA-active agents in 234 subjects with eight treatment failures. Benzodiazepines may not always effectively mitigate tachycardia, hypertension, and vasospasm from cocaine toxicity" (p. 1). "The eight treatment failures were case reports with failure to attenuate hypertension and tachycardia" (p. 3). "Benzodiazepines are classified as Class I-B in a 2008 AHA scientific statement on cocaine-associated chest pain and myocardial infarction, and Class IIa-C in the most recent ACC/AHA guideline for the management of non-ST-elevation acute coronary syndrome" (p. 3).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Beta-blockers

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Adverse events	N/A	Systematic review: Richards 2015 [2] Moderate	"There were 9 high-quality clinical studies, 10 case series/reports, with 227 total subjects involving the use of beta-blockers with concomitant ARDA, and one putative case of "unopposed alpha-stimulation." This proportion loosely suggests an incidence rate of only 0.4%. If, however, there is a theoretical or real risk of "unopposed -stimulation" in the setting of toxicity from ARDA, then treatment with the combined - and -blockers labetalol or carvedilol is a logical choice. The use of labetalol for treatment of cocaine- and methamphetamine-associated chest pain has been included by the ACCF/AHA in their most recent2012 guidelines (Supplement 34) as Class IIb-C (Anderson et al.,2013)" (p. 10). "Two case reports were identified in which beta-blockers in the presence of ARDA were implicated in acute coronary vasoconstriction. Detailed analysis of these cases show otherwise" (p. 9).	
		Systematic review: Richards 2016 [1] Low	"Of the 1744 total patients identified in this systematic review, only seven adverse events were from putative cases of ''unopposed a-stimulation'' due to the b1/b2-blocker propranolol (n=3), and b1-blockers esmolol (n=3), and metoprolol (n=1). No cases were attributed to the use of mixed b1/b2/a1-blockers" (p. 15). "No adverse	

			events were reported for use of combined b/a-blockers such as labetalol and carvedilol" (p. 1).	
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015 [2] Moderate	"There were 14 high-quality (levels I, II) human studies" (p. 8). "For the ARDA-induced hyperadrenergic state, treatment with beta-blockers is a reasonable choice" (p. 10).	
		Systematic review: Richards 2016 [1] Low	**Beta-blockers and b/a blockers:** "There were nine Level I/II, seven Level III, and 34 Level IV/V studies of b-blockers, with 1744 subjects, seven adverse drug events, and three treatment failures. No adverse events were reported for use of combined b/a-blockers such as labetalol and carvedilol, which were effective in attenuating both hypertension and tachycardia" (p. 1). "The use of labetalol for treatment of cocaine-associated chest pain is designated Class IIb-C in the 2013 ACC/AHA guideline focused update for the management of non-ST-elevation acute coronary syndrome" (p. 14).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Nitric oxide-mediated vasodilators

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Adverse events	N/A	Systematic review: Richards 2016[1] Low	Nitroglycerin • 6 Level I/II, 1 Level III, 25 Level IV/V studies (n=246 subjects) • Adverse drug events: Severe hypotension (n=2). • "Nitroglycerin may lead to severe hypotension and reflex tachycardia" (p. 1).	
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015 [2] Moderate	For nitroglycerin • 4 case reports • "Nitroglycerin is recommended as ACCF/AHA Class I-C for treatment of cocaine and ARDA-associated chest pain but should be given with the recognition it may result in reflex tachycardia." (p. 10). For nitroprusside • 2 case reports • "Nitroprusside may ameliorate peripheral arterial vasospasm and hypertension, but no clinical studies exist at present" (p. 10).	ARDA-induced hyperadrenergic state.

		Systematic review: Richards 2016 [1] Low	Nitroglycerin • 6 Level I/II, 1 Level III, 25 Level IV/V studies (n=246 subjects) • 11 treatment failures: "nitroglycerin did not reduce blood pressure and heart rate in five case reports. There was a failure to mitigate chest pain and/or vasospasm in five case reports. Finally, there was one failure to resolve a cocaine-associated hypertensive emergency with nitroprusside" (p. 7).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Calcium channel blockers

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important/Critical Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2015 [2] Moderate	Three level II evidence studies, one case series, three case reports on the use of calcium channel blockers for toxicity from ARDA. "Calcium channel blockers are a reasonable choice to treat ARDA-induced hypertension, but not necessarily tachycardia. However the number of studies is small. The dihydropyridine-class calcium channel blockers such as nifedipine and amlodipine are more likely to result in reflex tachycardia compared to the benzothiazepine-and phenylalkylamine-class agents such as diltiazem and verapamil (Olson, 2013). The current ACCF/AHA guidelines include recommendations for IV or oral calcium channel blockers as Class I-C in the setting of chest pain with ST-segment changes, and Class IIa-C for chest pain without ST-segment changes" (p. 10).	
		Systematic review: Richards 2016[1] Low	"There were seven Level I/II, one Level III, and seven Level IV/V studies involving 107 subjects and one treatment failure. Calcium channel blockers may decrease hypertension and coronary vasospasm, but not necessarily tachycardia" (p. 1). "The 2013 ACC/AHA guideline focused update on the management of non-ST-elevation acute coronary syndrome includes recommendations for oral or IV calcium channel blockers as Class I-C in the setting of cocaine-induced chest pain with ST-segment changes, and Class IIa-C for chest pain without ST-segment changes.[" (p. 7).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Other agents

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Important Outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	N/A	Systematic review: Richards 2016 [1] Low	"There was only one high level study of morphine, which reversed cocaine-induced coronary vasoconstriction but increased heart rate. Other agents reviewed included lidocaine, sodium bicarbonate, amiodarone, procainamide, propofol, intravenous lipid emulsion, propofol, and ketamine" (p. 1).	

[i] SOE: The strength of evidence is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
[ii] Quality of MAs and SRs evaluating using AMSTAR-2 instrument (Shea et al., 2017)

Existing Guidelines

Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. *J Am Coll Cardiol*. 2021;78(22):e187-e285. doi:10.1016/j.jacc.2021.07.053

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

NSW Health. *Handbook for Nurses and Midwives: Responding Effectively to People Who Use Alcohol and Other Drugs*. CPH 210385. New South Wales Ministry of Health; 2021. Accessed September 16, 2021. www.health.nsw.gov.au

Holmwood C, Gowing L. *Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults*. Clinical Guideline No. CG284. Drug and Alcohol Services South Australia (DASSA); 2019. https://www.sahealth.sa.gov.au/wps/wcm/connect/Public%20Content/SA%20Health%20Internet/Resources/Policies/Acute%20Presentations%20Related%20to%20Methamphetamine%20Use%20Clinical%20Guideline

Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. *J Am Coll Cardiol*. 2014;64(24):e139-e228. doi:10.1016/j.jacc.2014.09.017

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;62(16):e147-e239. doi:10.1016/j.jacc.2013.05.019

Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(23):e663-e828.

McCord J, Jneid H, Hollander JE, et al. Management of Cocaine-Associated Chest Pain and Myocardial Infarction: A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117(14):1897-1907. doi:10.1161/CIRCULATIONAHA.107.188950

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Other reviews

Gresnigt FMJ, Gubbels NP, Riezebos RK. The current practice for cocaine-associated chest pain in the Netherlands. *Toxicol Rep*. 2021;8:23-27. doi:10/gn763q
Duflou J. Psychostimulant use disorder and the heart. *Addiction*. 2020;115(1):175-183. doi:10.1111/add.14713

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	
Systematic review: Richards 2015[2] Moderate "Benzodiazepines may be useful in ARDA-precipitated chest pain alone or in combination with nitroglycerin, although this is based on cocaine studies as none exist for ARDA" (p. 10). Systematic review: Richards 2016[1] Low Benzodiazepines are classified as Class I-B in a 2008 AHA scientific statement on cocaine-associated chest pain and myocardial infarction, and Class IIa-C in the most recent ACC/AHA guideline for the management of non-ST-elevation acute coronary syndrome" (p. 3). Evidence is primarily for BZDs. Evidence for propofol was not found.	During stimulant intoxication ACS/chest pain outside intoxication or not responding to GABA-active agents, treat similarly to non-stimulant related chest pain with caution of BB use. Recommendation for propofol is from presumed benefit in the intoxicated state for severe agitation.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Richards 2015[2] systemic review background info notes Over-sedation and respiratory depression are a risk of large and repeated doses of benzodiazepines (Forster et al., 1980). Paradoxical agitation is another potential adverse effect (Short et al., 1987)" (p. 3). The theoretical risk of oversedation and paradoxical agitation was not observed in the two systematic reviews (Richards 2015[2] and 2016[1])	Assumes that BZDs are used appropriately	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence shows GABA-active agents, BZ primarily, to be a consideration for CP related to stimulant use with same studies indicating overall safety when used appropriately		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison

		☐ Varies ☐ Don't know
Certainty/Quality of Evidence: Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
There was one moderate quality systematic review Better data for BZDs and cocaine Animal studies BZDs for ATStUD less studied		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
*** Values and preferences:** Confidence and variability in values and preferences of stakeholders. Is there important variability in how much people value the main outcomes? Is there uncertainty about how much people value the main outcomes?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no **(x)** ☒ Uncertain ☐ Probably yes ☐ Yes
***Equity:** What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability:** Is the option acceptable to key stakeholders (patients, caregivers, providers)?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Studies indicate the use of benzodiazepines and other GABA-active agents are beneficial and relatively safe in managing chest pain during stimulant intoxication.

Subgroup Considerations

Risk of cardiovascular disease is higher in some populations, which increases the risk that cocaine toxicity will exacerbate them

Implementation Considerations

- If medications are used, clinicians should monitor patients for medication side effects according to standard care.
    - Patients treated with benzodiazepines should be monitored for side effects such as sedation, confusion, delirium, and other known side effects of benzodiazepines.
- Propofol can be used in ICU settings
- If chest pain is not responding or not resolving, clinicians can consider concomitant treatment with one of the adjunct medications recommended for persistent hyperadrenergic symptoms.

References

1. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10/gfv25h
2. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10/f69r7s
3. Connors NJ, Alsakha A, Larocque A, Hoffman RS, Landry T, Gosselin S. Antipsychotics for the treatment of sympathomimetic toxicity: A systematic review. *Am J Emerg Med*. 2019;37(10):1880-1890. doi:10.1016/j.ajem.2019.01.001
4. Kishi T, Matsuda Y, Iwata N, Correll CU. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2013;74(12):e1169-1180. doi:10/gn76x9
5. Indave BI, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online March 19, 2016. doi:10/f8gwnx
6. Lee N, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018;191:309-337. doi:10/gfw5px

7. Shoptaw SJ, Kao U, Ling W. Treatment for amphetamine psychosis. Cochrane Drugs and Alcohol Group, ed. *Cochrane Database Syst Rev*. Published online January 21, 2009. doi:10/dg2tpm

Table 42. Chest Pain Management of Cardiac Ischemia

Recommendation: Alternative agents (eg, calcium channel blockers, vasodilators) are generally preferred for management of cardiac ischemia in patients experiencing stimulant intoxication. However, if beta blockers are used in patients with stimulant intoxication, clinicians should consider using a medication with concomitant alpha 1 antagonism (eg, carvedilol, labetalol). If an unopposed beta blocker was used in a patient who is or was recently stimulant intoxicated, clinicians should also consider providing a coronary vasodilator (eg, nitroglycerin, calcium channel blocker). For complex cases, consult with cardiology and/or toxicology.

Clinical Question Summary

Clinical Question	1. What is the effectiveness of beta-blockers for managing the cardiac consequences of stimulant intoxication? 2. Can beta-blockers be used safely to treat chest pain in patients experiencing stimulant intoxication?
Population	Acute cocaine or amphetamine-type stimulant intoxication, experiencing chest pain
Intervention	Beta-blockers or beta/alpha blockers
Comparison	No beta-blockers or beta/alpha blockers (no medication or other medication)
Main Outcomes	Adverse events, cardiac symptom reduction
Setting	Hospital, Emergency department, psychiatric urgent care centers
Background& Definitions	Chest pain and MI outcome health disparities The cardiac complications of stimulant use include chest pain, with elevated risks for acute coronary syndrome and cardiac related mortality. Hyperadrenergic states, secondary to stimulant use, can lead to hypertension and tachycardia.
Abbreviations	**Amph:** Amphetamine, **N:** Number, **RoB:** Risk of Bias, **RR:** Risk ratio, **CI:** Confidence interval, **RCT:** Randomized control trial, **ARDA:** Amphetamine, related derivatives, and analogues, **ACC:** American College of Cardiology, **AHA:** American Heart Association, **MA:** Methamphetamine, **SoE:** Strength of evidence, **HTN:** Hypertension, **MI:** Myocardial infarction, **GABA:** Gamma aminobutyric acid, **HIV:** Human immunodeficiency virus
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critically important outcomes				
All-cause mortality	Low	Meta-analysis: Lo 2019[1] (Not assessed)	**No difference** in all-cause mortality between patients with cocaine-induced chest pain treated with or without beta-blockers **4 studies**, 1072 patients, RR=0.75; 95% CI (0.46, 1.24). • Datillo (2008), Fanari (2014), Rangel (2010), Schmidt (2015)	All retrospective studies, two with paired/matched controls.
		Meta-analysis: Shin 2019[2] (Critically low)	No difference in in-hospital all-cause mortality in patients presenting with cocaine-associated chest pain or recent cocaine use treated with beta-blockers vs not treated with beta-blockers: **4 studies**, 1071 patients, RR=0.59, 95% CI (0.24, 1.47). • Cediel (2018), Datillo (2008), Fanari (2014), Rangel (2010). No difference in all-cause mortality rate at follow-up (mean follow-up 2.6 years): **3 studies**, 572 participants, RR= 0.79, 95% CI (0.44, 1.41) • Cediel (2018), Finks (2015), Rangel (2010)	All observational studies. One prospective (Cediel, 2018).
		Meta-analysis: Pham 2018[3]	**No significant difference** between patients treated with beta-blocker vs no beta-blocker in all-cause mortality rate in patients presenting to the ED with cocaine-associated chest pain (3 studies, n=1014, 6/348 [1.7%] vs 22/666 [3.3%], OR 0.68, 95% CI 0.26-1.79, p=0.43) without significant heterogeneity between studies (I-squared=0%, p=0.98). • Datillo 2008 (n=310, cardioselective beta1-blockers 66%, Newcastle-Ottowa scale=7) • Fanari 2014 (n=376, cardioselective beta1-blockers 47%, Newcastle-Ottowa scale=8) • Rangel 2010 (n=328, cardioselective beta1-blockers 87%, Newcastle-Ottowa scale=8) Significant baseline differences between patients treated with beta-blockers and those not treated with beta-blockers: Beta-blocker group was older, more likely to be African American, have hypertension, diabetes mellitus, coronary artery disease, hyperlipidaemia, prior congestive heart failure, higher serum creatinine, less likely to have lung disease (COPD/asthma)	All non-random retrospective observational studies
Myocardial infarction	Low	Meta-analysis: Lo 2019[1] (Not assessed)	No difference in myocardial infarction risk between patients with cocaine-induced chest pain treated with or without beta-blockers: 5 studies, 1447 patients, RR=1.08, 95% CI (0.61, 1.91). • Datillo (2008), Fanari (2014), Ibrahim (2013), Rangel (2010), Schmidt (2015)	All retrospective studies, two with paired/matched controls.

		Meta-analysis: Shin 2019[2] (Critically low)	No difference in in-hospital myocardial infarction or myocardial necrosis in patients presenting with cocaine-associated chest pain or recent cocaine use treated with beta-blockers vs not treated with beta-blockers: 6 studies, 1805 patients, RR= 1.24, 95% CI (0.74, 2.06). However, heterogeneity was significant (I^2= 63, p=0.019). • Datillo (2008), Fanari (2014), Ibrahim (2013), Mohamad (2008), Rangel (2010), Schmidt (2015). Also no difference in all-cause mortality rate at follow-up (mean follow-up 2.6 years): 2 studies, 244 participants, RR= 0.96, 95% CI (0.40, 2.33). • Cediel (2018), Finks (2015)	All observational studies. One prospective (Cediel, 2018).
		Meta-analysis: Pham 2018[3]	**No significant difference** between patients treated with beta-blocker vs no beta-blocker in rate of non-fatal myocardial infarction (MI) in patients presenting to the ED with cocaine-associated chest pain (5 studies, n=1794, 94/610 [15.4%] vs 162/1146 [14.1%], OR 1.36, 95% CI 0.68-2.75, p=0.39), although there was significant heterogeneity between studies (I-squared=71%, p=0.008) • Datillo 2008 (n=310, cardioselective beta1-blockers 66%, Newcastle-Ottowa scale=7) • Fanari 2014 (n=376, cardioselective beta1-blockers 47%, Newcastle-Ottowa scale=8) • Ibrahim 2012 (n=378, cardioselective beta1-blockers 61%, Newcastle-Ottowa scale=8) • Mohamad 2008 (n=364, Newcastle-Ottowa scale=7) • Rangel 2010 (n=328, cardioselective beta1-blockers 87%, Newcastle-Ottowa scale=8) Significant baseline differences between patients treated with beta-blockers and those not treated with beta-blockers: Beta-blocker group was older, more likely to be African American, have hypertension, diabetes mellitus, coronary artery disease, hyperlipidaemia, prior congestive heart failure, higher serum creatinine, less likely to have lung disease (COPD/asthma)	All non-random retrospective observational studies
Treatment failure	Low	Systematic review: Richards 2016[4] (Low)	Three treatment failures reported in 50 studies of beta-blockers and cocaine toxicity with or without chest pain (n=1744). Treatment failures were defined by no significant effect of the study drug on evaluated parameters and/or no change in clinical outcomes for case series and reports.	RCTs accounted for only 69 of 1744 participants
Important outcomes				
Hyperadrenergic symptoms (hypertension, tachycardia)	Low	Systematic review: Richards 2015[5] (Moderate)	"There were 14 high-quality (levels I, II) human studies" (p. 8). "For the [amphetamines, related derivatives, and analogues] ARDA-induced hyperadrenergic state, treatment with-blockers is a reasonable choice... If, however, there is a theoretical or real risk of 'unopposed alpha-stimulation' in the setting of toxicity from ARDA, then treatment with the combined alpha- and beta-blockers labetalol or carvedilol is a logical choice" (Richards, 2015 p 10).	

		Systematic review: Richards 2016[4] (Low)	"There were nine Level I/II, seven Level III, and 34 Level IV/V studies of b-blockers, with 1744 subjects" (p. 1). "Combined b/a-blockers such as labetalol and carvedilol... were effective in attenuating both hypertension and tachycardia" (Richards, 2016 p 1). "The use of labetalol for treatment of cocaine-associated chest pain is designated Class IIb-C in the 2013 ACC/AHA guideline focused update for the management of non-ST-elevation acute coronary syndrome" (p. 14).	
Adverse events	Low	Systematic review: Richards 2015[5] (Moderate)	1 putative case of ''unopposed alpha-stimulation'' due to b1-blocker practolol reported in 19 studies with 227 participants with amphetamine-type stimulant toxicity with or without chest pain.	
		Systematic review: Richards 2016[4] (Low)	7 putative cases of ''unopposed alpha-stimulation'' due to the b1/b2-blocker propranolol (n=3), and b1-blockers esmolol (n=3), and metoprolol (n=1) reported in 50 studies of beta-blockers and cocaine toxicity with or without chest pain (n=1744). No adverse events were reported specifically from the use of the combined b1/b2/a1-blockers labetalol or carvedilol (21 studies, 632 patients).	

Existing Guidelines

Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes. *J Am Coll Cardiol*. 2014;64(24):e139-e228. doi:10.1016/j.jacc.2014.09.017

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

McCord J, Jneid H, Hollander JE, et al. Management of Cocaine-Associated Chest Pain and Myocardial Infarction: A Scientific Statement From the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117(14):1897-1907. doi:10.1161/CIRCULATIONAHA.107.188950

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;62(16):e147-e239. doi:10.1016/j.jacc.2013.05.

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Research is primarily from uncontrolled studied where patients on beta-blockers are also generally sicker than patients not on beta-blockers. One angiogram study showed vasospasm	For beta blockers, the evidence is small to moderate. For alpha-beta combinations, there was small amount of evidence that showed favorable outcomes with labetolol/carvedolol	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Reducing risk or myocardial infarction and cardiac-related or all-cause mortality is important. However, the studies examined found no effect on reducing the risk of either MI or death with the use of beta-blockers Unopposed beta-blockers vs alpha-beta combo or beta + vasodilator No beta-blocker vs Alpha-beta combo or beta-blocker + vasodialator: No clear evidence that beta-blockers improve outcome (mortality/MI, so ACS whether cocaine induced or otherwise) in those individuals with cocaine intoxication and chest pain.		
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
The concern of unopposed alpha stimulation following the use of beta blockers in the setting of stimulant toxicity remains.		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Risks outweigh the benefits of routine use of beta blockers to treat patients with concomitant chest pain and stimulant toxicity.	There is some evidence supporting treating hyperadrenergic states leading to hypertension and tachycardiac with combined beta 1/2 and alpha-blockade medications (eg, labetalol or carvedilol). Labetolol has less alpha blockade than beta blockade but some studies have shown benefits with either carvedilol or labetolol (low quality). Treatment of the HTN and tachycardia may lead to less chest pain and risk MI if mixed alpha/beta.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence is solely observational studies	Small number of patients in RCTs, otherwise mostly retrospective reviews or observational studies.	☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** there important variability in how much people value the main outcomes? Is there uncertainty about how much people value the main outcomes?		
Evidence Summary	*Additional Considerations*	*Judgment*
No clear evidence	Considerable value in value and preferences assuming the outcome is treatment of chest pain and MI due to stimulant intoxication without exacerbating toxicity. The debate over beta blocker risk (vs use dual alpha-beta) vs simply using GABAergic agents is ongoing.	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity:** What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
No clear evidence	Health inequities are possible given systemic issues in US health care delivery. There is evidence for higher risk of adverse cardiac outcomes in general for diverse populations primarily related to prior access to care, mistrust healthcare system, etc. Morbidity and mortality related to cocaine use higher with HIV, AA (with HIV in one study) but this is not clearly related to risk then with beta-blocker use for chest pain.	☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability:** Is the option acceptable to key stakeholders (patients, caregivers, providers)?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

For the primary diagnosis of chest pain in patients with cocaine or stimulant use, observational review studies have shown no difference in all-cause mortality between patients treated with or without beta blockers (low quality evidence). Combined beta- and alpha-adrenergic antagonism may have some utility in reducing hyper-adrenergic states in these patients.
Coronary vasodilators counter the side effect of unopposed alpha stimulation, coronary vasospasm.
Alpha/beta-blockade vs alpha-blockade
Selective beta-blockers are preferred to unselective (bi-lateral) beta-blockers.
Clinical situations: If already taking/received a coronary vasodilator (eg, because you were following MI protocol, angina), could use an unopposed beta-blocker.

Subgroup Considerations

Risk of cardiovascular disease is higher in some populations, which increases the risk that cocaine toxicity will exacerbate them

Implementation Considerations

Beta blockers are generally contraindicated in patients with cocaine intoxication and cardiovascular disease; this is an area of ongoing controversy in the field. Many experts recommend alternative medications such as calcium channel blockers, alpha-1 adrenergic antagonists, alpha-2 adrenergic agonists, and nitric oxide-mediated vasodilators, as symptoms indicate, to achieve similar effects in patients with stimulant intoxication.

References

1. Lo KB, Virk HUH, Lakhter V, et al. Clinical Outcomes After Treatment of Cocaine-Induced Chest Pain with Beta-Blockers: A Systematic Review and Meta-Analysis. *Am J Med*. 2019;132(4):505-509. doi:10/gn757k
2. Shin D, Lee ES, Bohra C, Kongpakpaisarn K. In-hospital and long-term outcomes of beta-blocker treatment in cocaine users: A systematic review and meta-analysis. *Cardiol Res*. 2019;10(1):40-47. doi:10.14740/cr831
3. Pham D, Addison D, Kayani W, et al. Outcomes of beta blocker use in cocaine-associated chest pain: a meta-analysis. *Emerg Med J.* 2018;35(9):559-563. doi:10.1136/emermed-2017-207065
4. Richards JR, Garber D, Laurin EG, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clin Toxicol Phila Pa*. 2016;54(5):345-364. doi:10/gfv25h
5. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1-13. doi:10/f69r7s

Table 43. Chest Pain Evaluation

Recommendation: While treating underlying stimulant intoxication in patients experiencing chest pain, clinicians should concomitantly evaluate for acute coronary syndromes (ACS) and other causes of acute chest pain in stimulant intoxication (eg, pulmonary, musculoskeletal (MSK), etc.). Chest pain that does not fully resolve as signs and symptoms of stimulant intoxication improve should be evaluated and treated following current standards of care.

Clinical Question Summary

Clinical Question	Should the presence of stimulant intoxication impact the standard evaluation of chest pain?
Population	Patients with stimulant intoxication experiencing chest pain
Intervention	Variations on typical evaluation of chest pain
Main Outcomes	Successful management of chest pain
Setting	Acute care settings such as ED
Background & Definitions	Cardiac complications of stimulant use include chest pain with elevated risks for acute coronary syndrome (ACS) and cardiac-related mortality. Hyperadrenergic states secondary to stimulant use can lead to hypertension and tachycardia.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No research was identified.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Desirable effects are avoiding cardiac death as a result of undiagnosed, unmanaged ACS. Substantial desirable effects associated with protecting cardiac health and managing ACS in accordance with standardized clinical pathways. Coronary constriction is more common with cocaine than ATS use. More studied in cocaine	Well studied and supported treatment pathways for management of ACS. Although less studied in ATS, substantial desirable effects anticipated.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Undesirable effects are those associated with treating underlying ACS, which include the generally mild side effects from some of the medications used (primarily beta-blockers). Individual medication side effect profiles as well as contraindications and interactions will determine the actual magnitude.		☐ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Risks of undertreated or mistreated ACS outweigh any risks of the medications used in standard of care management of ACS.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies

***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	There is existing inequity stemming from regional differences in hospitals' capability to provide high quality ACS services. This recommendation may require more sophisticated management, which may increase existing inequity. However, this recommendation could increase an underserved population's access to any ACS care, which could decrease health inequality.	☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Ability of the clinical system/setting to provide ACS services including staffing time and medication.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

ACS management currently has well accepted standards of care. The risk of mistreated or untreated ACS outweigh any potential risk of the medications that are utilized to manage ACS, even in the presence of stimulant use. Even if a patient has cocaine intoxication, if the sign symptoms of intoxication resolve or if the medical management that we describe in other recommendations is ineffective to reduce chest pain, we should be looking for other causes, particularly in acute coronary syndrome. Or, even regardless of non-response to treatment we should be looking for other causes. Certainty of evidence is moderate, based on well accepted standard of care and ACS management evidence.

Subgroup Considerations

There is existing inequity stemming from regional differences in hospitals' capability to provide high quality ACS services
Risk of cardiovascular disease is higher in some populations, which increases the risk that cocaine toxicity will exacerbate them

Implementation Considerations

Current standard of care example: 2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes.

Table 44. QRS Widening

Recommendation: Cocaine has local anesthetic-like effects at sodium channels and can cause QRS widening with impairment in cardiac contractility during severe cocaine intoxication. If these issues are identified, in addition to treating intoxication, clinicians should administer sodium bicarbonate to improve the conduction block and contractility; this will also improve metabolic acidosis if present.

Clinical Question Summary

Clinical Question	What are the most effective and appropriate interventions for the treatment of QRS widening following cocaine use?
Population	Patients with cocaine intoxication
Intervention	Treat with sodium bicarbonate
Comparison	TAU
Main Outcomes	Conduction block and contractility
Setting	Acute care settings such as ED
Background & Definitions	• MA-dependent adults (N = 301) interviewed and examined 3 years after treatment. A significant proportion of the sample evidenced prolonged corrected QT interval (19.6%, N = 43) (Mooney et al., 2009)
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No research was identified.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
In animal models and studies of cocaine toxicity, sodium bicarbonate improved blood pressure and myocardial function. Literature reviews on the use of sodium bicarbonate for QRS widening in humans where cocaine was identified as one of the causal factors.	Improvement in cardiac function is the main reason, but Correction of metabolic acidosis would also occur.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Can exacerbate risk for QT prolongation if present by lowering serum potassium concentrations.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
High agreement between animal models, reviews, case series, basic science (electrophysiologic studies).		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies

***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Risk of cardiovascular disease is higher in some populations, which increases the risk that cocaine toxicity will exacerbate them.	Appropriate treatment is likely to reduce existing inequity assuming widespread, equal implementation.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	There have been sodium bicarbonate shortages at times and 3% hypertonic saline has been used as a sodium replacement, but it doesn't have the effect on acid/base normalization.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusions

Justification

Cocaine has local anesthetic-like effects at sodium channels and can cause QRS widening with impairment in cardiac contractility during severe cocaine intoxication. If these issues are identified, in addition to treating intoxication, clinicians should administer sodium bicarbonate to improve the conduction block and contractility; this will also improve metabolic acidosis if present.

Subgroup Considerations

Risk of cardiovascular disease is higher in some populations, which increases the risk that cocaine toxicity will exacerbate them

Implementation Considerations

There have been sodium bicarbonate shortages at times and 3% hypertonic saline has been used as a sodium replacement, but it doesn't have the effect on acid/base normalization.

References

1. Mooney LJ, Glasner-Edwards S, Marinelli-Casey P, et al. Health conditions in methamphetamine-dependent adults 3 years after treatment. *J Addict Med*. 2009;*3*(3):155-163. https://doi.org/10.1097/ADM.0b013e3181a17c79

Table 45. Seizure Medication

Recommendation: For stimulant intoxication-related seizure or concomitant alcohol- or sedative- related seizures, clinicians should treat with a benzodiazepine.

a. If seizures are refractory to benzodiazepines, clinicians can consider treating with either phenobarbital or propofol.

Clinical Question Summary Table

Clinical Question	What are the most effective and appropriate interventions for the treatment of seizure following stimulant use?
Population	Patients with a seizure following stimulant use
Intervention	Benzodiazepines, phenobarbital or propofol
Comparison	No medication or comparison among the intervention medications
Main Outcomes	Adverse events, Recurrence of seizure
Setting	Emergency department
Background & Definitions	• One retrospective multi-center study of ER patients with seizures secondary to suspected cocaine use found that most cocaine-associated seizures are self-limited (Majlesi et al 2010). Of 43 patients in the ED for cocaine-associated seizures, 42 experienced a single tonic-clonic seizure and one developed status epilepticus.
Abbreviations	**N/A**: Not applicable, **MDMA:** 3,4-methylenedioxymethamphetamine, **SoE:** Strength of evidence
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Findings Table

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality)[ii]	Effect/Impact	Comments
Adverse events	Important	N/A	None found		
Recurrence of seizure	Important	N/A	None found		

[i]: Strength of evidence (SOE) categories: High = further research is very unlikely to change confidence on the estimate of effect. Moderate = further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.

Existing Guidelines

Holmwood C, Gowing L. *Acute Presentations Related to Methamphetamine Use: Clinical Guideline for Adults*. Clinical Guideline No. CG284. Drug and Alcohol Services South Australia (DASSA); 2019. https://www.sahealth.sa.gov.au/wps/wcm/connect/Public%20Content/SA%20Health%20Internet/Resources/Policies/Acute%20Presentations%20Related%20to%20Methamphetamine%20Use%20Clinical%20Guideline

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.

Non-Systematic Reviews & Commentary

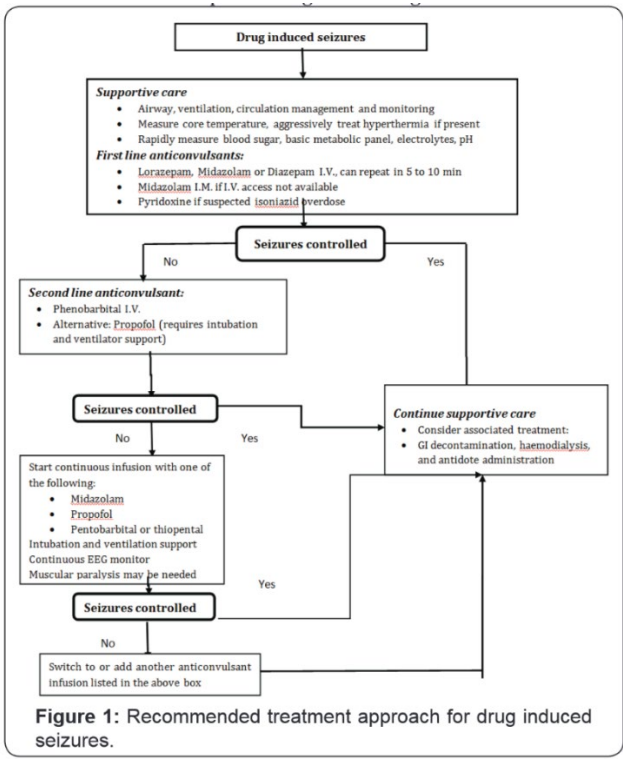
<table>
<tr><th>Source</th><th>Recommendation</th><th>Comments</th></tr>
<tr><td>Vaidya & Petare 2017[1]</td><td>


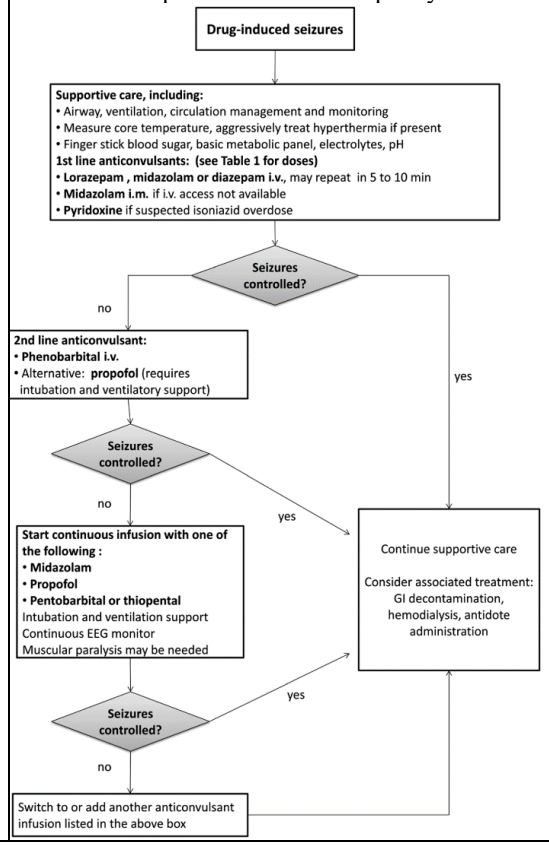
Figure 1: Recommended treatment approach for drug induced seizures.

Table 3: Anticonvulsants for drug induced seizures.

Drug	Initial/ Loading dose	Continuous infusion
Diazepam	5 – 10 mg IV (children: 0.2 to 0.5 mg/kg) over 2 to 5 min (max 10 mg/day); may repeat every 5 – 20 min	Note: contains propylene glycol
Lorazepam	2 - 4 mg IV (children: 0.05 to 0.1 mg/kg, max 4 mg/day); may repeat every 5 – 10 min (max rate: 2 mg/min)	Note: contains propylene glycol
Midazolam*	I.V.: 0.05 – 0.2 mg/kg (children: 0.1 – 0.3 mg/kg) over 20 – 30 sec (max 10 mg)	0.05 to 2 mg/kg/ hr titrated to EEG
Pentobarbital	I.M.: 0.1 – 0.2 mg/kg (max 10 mg)	0.05 to 2 mg/kg/ hr titrated to EEG
Phenobarbital	5 – 15 mg/kg I.V. (children: 3 -15 mg/kg) no faster than 1 mg/ kg/min	Note: contains propylene glycol
Propofol $	15 – 20 mg/kg I.V. no faster than 1 mg/kg/min. An additional 5 – 10 mg/kg dose may be given 10 min after initial dose	1.5 – 10 mg/kg titrated to EEG
Thiopental	1 -2 mg/kg I.V.	0.5 – 5 mg/kg/hr titrated to EEG
Thiopental	2 – 7 mg/kg I.V. no faster than 1 mg/kg/min	0.5 – 5 mg/kg/hr titrated to EEG

*Consider I.M. route when there is no I.V. access
$ - Propofol is not recommended for infants and young children.</td><td>Not stimulant specific</td></tr>
<tr><td>Chen 2016[1]</td><td>Treatment of drug-induced seizures</td><td>Not stimulant specific</td></tr>
</table>

- "Benzodiazepines are the first-line treatment for drug-induced seizures, with addition of pyridoxine if isoniazid or other hydrazine toxicity is suspected. If benzodiazepines fail to terminate seizures, second-line agents include barbiturates and propofol. There is no role for phenytoin in the management of drug-induced seizures. The role of valproic acid, levetiracetam, ketamine, adenosine agonists and other drugs is not established." (Chen et al., 2016, p. 417)
- "We were unable to find any randomized controlled trial or prospective study regarding the effectiveness of benzodiazepines specifically for drug-induced seizures. However, a Cochrane review and a large randomized controlled trial for status epilepticus of any cause found that intravenous lorazepam was better than intravenous diazepam or intravenous phenytoin alone for cessation of status epilepticus [35, 36]." (Chen et al., 2016, p. 414)



Anticonvulsants for drug-induced seizures [48, 78, 79]

Drug	Initial/Loading dose	Continuous infusion
Diazepam	5–10 mg i.v. (children: 0.2–0.5 mg kg^{-1}) over 2–5 min (max 10 mg/dose); may repeat every 5–20 min.	Note: contains propylene glycol.
Lorazepam	2–4 mg i.v. (children: 0.05–0.1 mg kg^{-1}, max 4 mg/dose); may repeat every 5–10 min (max rate: 2 mg min^{-1}).	Note: contains propylene glycol.
Midazolam*	i.v.: 0.05–0.2 mg kg^{-1} (children: 0.1–0.3 mg kg^{-1}) over 20–30 s (max 10 mg). i.m.*: 0.1–0.2 mg kg^{-1} (max 10 mg).	0.05–2 mg kg^{-1} h^{-1} titrated to EEG.
Pentobarbital†	5–15 mg kg^{-1} i.v. (children: 3–15 mg kg^{-1}) no faster than 1 mg kg^{-1} min^{-1}.	0.5–5 mg kg^{-1} h^{-1}, titrated to EEG.
Phenobarbital†	15–20 mg kg^{-1} i.v. no faster than 1 mg kg^{-1} min^{-1}. An additional 5–10 mg kg^{-1} dose may be given 10 min after initial dose.	Note: contains propylene glycol.
Propofol†,‡	1–2 mg kg^{-1} i.v.	1.5–10 mg kg^{-1} h^{-1} titrated to EEG. Note: doses >5 mg kg^{-1} h^{-1} over prolonged periods may increase risk of propofol infusion syndrome.
Thiopental†	2–7 mg kg^{-1} i.v. no faster than 1 mg kg^{-1} min^{-1}.	0.5–5 mg kg^{-1} h^{-1} titrated to EEG.

*Consider intramuscular route when there is no i.v. access. †May cause deep sedation requiring endotracheal intubation. ‡Propofol is not recommended for infants and young children. [78]

Evidence to Decision Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
While no human studies, basic science/animal research on stimulant-induced seizures show greater efficacy in reducing seizure for GABAergic agents compared to standard anticonvulsant agents or sodium-channel blockers. Benzodiazepines are generally preferred as the initial treatment because of their relative wider availability and ease of use, rather than demonstrated superior effectiveness.	The recommendation is standard treatment for intoxication or withdrawal-related seizures, and is expected to be as effective for stimulants, assuming there is no other metabolic or underlying cause of seizure. Reduce recurrence of seizure.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Research Evidence	*Additional Considerations*	*Judgment*
	Risk of undersedation (not controlling the seizure) vs over-sedation (Side effects from medication) can occur depending on seizure type/context/severity, patient comorbidities and skill of the provider.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence	*Additional Considerations*	*Judgment*
	Undesirable effects can be anticipated and are tolerable given the harm of recurrent seizure.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence	*Additional Considerations*	*Judgment*
See desirable effects.		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Confidence and variability in values and preferences of stakeholders. Is there important variability in how much people value the main outcomes? Is there uncertainty about how much people value the main outcomes?		
Research Evidence	*Additional Considerations*	*Judgment*
		☒ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Equity:** What would be the impact on health inequities?		
Research Evidence	*Additional Considerations*	*Judgment*
	No anticipated impact	☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies

***Acceptability:** Is the option acceptable to key stakeholders (patients, caregivers, providers)?		
Research Evidence	*Additional Considerations*	*Judgment*
	Current standard practice.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence	*Additional Considerations*	*Judgment*
	Current standard practice.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

While the recommendations below reflect standard treatment for any toxicity- or withdrawal-related seizures, the CGC included it in this Guideline because of its importance in this patient population

Subgroup Considerations

In cases where a seizure is associated with a complication of stimulant use (eg, hyponatremia, trauma) rather than stimulant toxicity, standard treatments should be provided, including standard seizure medications when indicated.

Implementation Considerations

- Patients should be monitored for over-sedation
- Provider education on appropriate dosing and titration
- Use order sets for withdrawal seizures, including with there are medication shortages

References

1. Vaidya PH, Petare AU. Drugs implicated in seizures and its management. *J Pharmacol Clin Res*. 2017;3(2). doi:10.19080/JPCR.2017.03.555607
2. Chen HY, Albertson TE, Olson KR. Treatment of drug-induced seizures. *Br J Clin Pharmacol*. 2016;81(3):412-419. doi:10/f8b7r5

Table 46. Screening, Brief Intervention, & Referral to Treatment (SBIRT)

Recommendation: Clinicians should screen patients for StUD and engage patients in brief interventions using motivational interviewing or enhancement techniques to facilitate referral for an assessment for StUD, if indicated.

Clinical Question Summary

Clinical Question	1. How accurate are drug use screening instruments for risky stimulant use? 2. Does screening for stimulant use reduce stimulant use or improve other risky behaviors? 3. What are the harms of screening for risky stimulant use? 4. Do brief counseling interventions to reduce stimulant use, with or without referral, reduce stimulant use or improve other risky behaviors in patients with a positive screen? 5. What are the harms of brief interventions to reduce stimulant use in patients with a positive screen?
Population	Adolescent and adult patients who present with stimulant intoxication or withdrawal
Intervention	Screening for risky stimulant use with frequency-based and risk assessment tools
Comparison	Don't screen
Main Outcomes	Stimulant use, risky behavior, harms of screening, identification of risky stimulant use
Setting	Settings where stimulant intoxicated patients are encountered (specialty addiction treatment, emergency departments)
Background & Definitions	Notes: • A nationally representative survey of Australian adults estimated that 50.4% of stimulant users would develop a stimulant use disorder within 14 years of onset of use (Marel et al., 2019). Pre-existing mental disorders were significantly associated with increased risk.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analyses

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Overdose risk behavior	N/A	Review of reviews: Farrell	**Screening and Brief Intervention** • **Decreased** overdose risk behaviors IRR=0.72, 95% CI 0.59–0.87 ○ Bohnert 2016 (OUD, Brief motivational interviewing)	Review focused on **stimulant related** harms.

		2019[1] (Supplemental)	• Review rating of evidence: **Level of evidence: B*** (evidence from one or two RCTs only. *Evidence drawn from people who inject drugs and not specific to stimulant users, however we have no reason to believe this intervention would operate differently among stimulant users specifically.	Opioid users
Stimulant use	N/A	Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use** vs Other Intervention (attentional control/wait-list/TAU) in **primary care** Included study designs: RCTs, case-crossover trials Identified studies all of non-screen detected populations (ie, tx/help-seeking) • **No effect** on stimulant abstinence rate at 6-12 months (4 RCTs, RR 1.45, 95% CI 0.86-2.56) with significant heterogeneity (I^2=65%, p=0.03). o Baker 2001 (RCT, n=64 community-recruited Australian adult regular ATS use, 4-session in-person MI/CBT vs Control) o Baker 2005 (RCT, n=215 community-recruited Australian adult regular ATS use, 2-session in-person MI/CBT vs Control) o Marsden 2006 (RCT, n=342 community-recruited UK adolescent & young adult regular stimulant use, 1-session in-person MI vs Control) o Tait 2015 (RCT, n=160 community-recruited Australian young adult ATS use, 3-session computer-delivered MET/CBT vs Wait-list) • **No effect** on cocaine use days at 6-12 months (1 RCT, MD −0.47, 95% CI −1.17 to 0.24) o Stein 2009 (RCT, n=198 community-recruited US adult regular cocaine use, 4-session in-person MI vs Control) • **No effect** on amphetamine use severity (1 trial, SMD 0.10, 95% CI −0.35 to 0.54) o Tait 2015 (RCT, n=160 community-recruited Australian young adult ATS use, 3-session computer-delivered MET/CBT vs Wait-list)	USPSTF systematic review of screening in primary care.
		Review of reviews: Farrell 2019[1] (Supplemental)	**Screening and Brief Intervention** • **No effect** on reducing stimulant use based on 1 RCT o Saitz 2014 (RCT, n=528 adults risky drug use [19% cocaine] Primary Care, Screening + MI vs Screening + BNI vs Screening alone) • Review rating of evidence: **Level of evidence: B** (evidence from one or two randomized controlled trials only)	
		Meta-analysis: Sayegh 2017[3] (Moderate)	**Motivational Interviewing** • **No effect** on UDS-confirmed stimulant use 0-3 months following the intervention across 3 studies (d= -0.15, 95% CI –0.46 to 0.17p=0.37). o Ingersoll 2011 (n=54 community-recruited HIV+ who use crack cocaine [92% CoUD], 6-session MI vs Education Control) NSD bn groups @ 3 or 6 mo (d= -0.27 [-0.88, 0.35]) o McKee 2007 (n=74 tx seeking CoUD/abuse, 3-session CBT vs CBT+ 1-session MI-based MET) d= -0.24 [-0.75, 0.28]	

			○ Rohsenow 2004 (n=165 CoUD in hospital-based day treatment, 2x2 2-session individual MET vs Control followed by 4-session group coping-skills training (CST) vs Control, 12 months) NSD between groups (d=0.05 [-0.49, 0.59]), but MET was more effective for patients with low initial motivation while Control was more effective for patients with high initial motivation in self-reported cocaine use days at 1 year follow-up. "programs that provide MET [at the start of an intensive tx program] should probably provide it only to patients who are less motivated to change." (p. 11). Group CST was more effective in reduced cocaine use frequency at 1 year compared to control in women, but not overall.	
Important Outcomes				
Drug use	N/A	Meta-analysis: Tanner-Smith 2022[4] (Supplemental)	**Drug-targeted brief interventions** vs less active comparison condition (no treatment, sham, TAU) **in general medical settings** • **Decreased** multiple drug/mixed substance use (16 RCTs, SMD 0.08, 95% CI 0.002-0.15; I^2= 27.28%). • Individual studies not listed.	

		Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use** vs Other Intervention (control/wait-list/TAU) **in primary care**
			Including results for screen-detected and non-screen detected populations
			○ **Higher** drug abstinence rate at 3- to 4-month follow-up (15 trials, n=3636, 419/2134 vs 218/1502, RR 1.60, 95% CI 1.24-2.13; ARD=9%, 95% CI 5%-15%]; I^2=57%, p=0.001)
			○ No effect in screen-detected populations (8 trials, 203/1089 vs 148/823, RR 1.28, 95% CI 0.97-1.84, p=0.08; I^2=57%, p=0.022).
			  ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control)
			  ○ Gelberg 2017 (n=65 moderate-risk [ASSIST 4-26] drug using) [9% cocaine, 8% ATS] adults in primary care, 1-session in-person BI + 2 booster calls vs Attention Control)
			  ○ Ondersma 2007 (n=107 any illicit drug use in US women in hospital postdelivery recovery, 1-session computer MI + 2 booster mailings vs Assessment only)
			  ○ Ondersma 2014 (n=143 any drug use in US women in hospital postdelivery recovery, 1-session computer MET vs Attention Control)
			  ○ Ondersma 2018 (n=500 any [WIDUS ≥3] drug use in US women in hospital postdelivery recovery, 1-session computer BI on parenting vs Attention Control)
				USPSTF systematic review of screening in primary care.
				
				ARD = absolute risk difference
				ED=Emergency department
				Preg = Pregnant
				SMD = Standardized mean difference

			○ Tzilos Wernette 2018 (n=59 any [T-ACE or SURP-P] alcohol/drug use in pregnant women in OB/Gyn, 1-session computer MI + 1 booster vs Attention Control) ○ Yonkers 2012 (n=183 any [TWEAK ≥3] drug use in US pregnant women in Ob/Gyn, 6-session computer MET/CBT vs Brief Advice) ○ Zahradnik 2009 (n=126 Rx drug misuse/dependent German adults in hospital, 1 in-person MI + phone booster vs Control) ○ Positive effect in non-screen detected populations (treatment seeking) (7 trials, 216/1045 vs 70/679, RR=2.1, 05% CI 1.52-2.90, p<0.001; I-squared=28%, p=0.22) ○ Babor 2004 (n=450 cannabis dependent US adults, 9-session MET/CBT vs 2-session MET vs Waitlist) ○ Gates 2012 (n=149 cannabis using Australian adolescent/young adults, 4-session phone MI/CBT vs Waitlist) ○ McCambridge 2004 (n=200 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ Rooke 2013 (n=230 cannabis using Australian adults, 6-module web-based MI/CBT vs Control) ○ Schaub 2015 (n=308 cannabis using US adults, 8-module web-based MI/CBT w/ chat vs w/out chat vs Waitlist) ○ Stephens 2000 (n=291 cannabis using US adults, 14-session in-person CBT vs 2-session in-person MI vs Waitlist) ○ **Higher** drug abstinence rate at **6- to 12-month** follow-up (14 RCTs, n=4031, 535/2420 vs 352/1871, RR 1.31, 95% CI 1.10 to 1.55, p=0.002; I^2=38%, p=0.07; ARD=6%, 95% CI 2%-10%) ○ No effect in screen-detected populations (7 trials, 298/1687 vs 204 vs 1256, RR 1.17, 95% CI 0.99 to 1.38, p=0.06, I^2=2%, p=0.41) ○ Bernstein 2005 (n=1175 moderate-to-severe [DAST-10 ≥3] cocaine/heroin using [93% cocaine] US adults in primary care, 1 in-person MI + phone booster vs Control) ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) ○ Ondersma 2014 (n=143 any drug use in US women in hospital postdelivery recovery, 1-session computer MET vs Attention Control)	

			○ Ondersma 2018 (n=500 any [WIDUS ≥3] drug use in US women in hospital postdelivery recovery, 1-session computer BI on parenting vs Attention Control) ○ Saitz 2014 (RCT, n=528 risky [ASSIST ≥4] drug using [19% cocaine] US adults in primary care, Screening + MI vs Screening + BNI vs Screening alone) ○ Zahradnik 2009 (n=126 Rx drug misuse/dependent German adults in hospital, 1 in-person MI + phone booster vs Control) ○ Positive effect in non-screen detected populations (treatment seeking) (7 trials, 237/733 vs 148/615, RR 1.51, 95% CI 1.14 to 2.37, p=0.008; I^2=57%, p=0.03) ○ Baker 2001 (n=64 community-recruited stimulant using Australian adults, 4-session in-person MI/CBT vs Control) ○ Baker 2005 (n=215 community-recruited stimulant using Australian adults, 2-session in-person MI/CBT vs Control) ○ Copeland 2001 (n=173 cannabis using Australian adults, 1-session in-person vs Wait-list) ○ Marsden 2006 (RCT, n=342 community-recruited regular stimulant using UK adolescent/young adults, 1-session in-person MI vs Control) ○ McCambridge 2004 (n=200 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ Tait 2015 (RCT, n=160 community-recruited ATS using Australian young adults, 3-session computer-delivered MET/CBT vs Wait-list) ○ **Decreased** drug use days in the past 7 days at **3- to 4-month** follow-up (19 trials, n=5085, MD –0.49, 95% CI –0.85 to –0.13; I^2=89%, p<0.001). ○ In screen-detected populations (9 trials, n=3421, MD −0.10 [−0.31, 0.12]; I^2=45.8%, p=0.044). ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Blow 2017 (n=780 risky [ASSIST ≥4] drug using US adults in ED, 1-session in-person MI vs 1-session computer MI vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) ○ Lee 2010 (n=341 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Lee 2013 (n=212 cannabis using US college age students, 1-session in-person personalized feedback vs Control)	

			○ Martino 2018 (n=439 moderate risk [ASSIST 4-26] drug using women primary care reproductive health visit, 1-session in-person BI vs 1-session computer BI vs Control) ○ Palfai 2014 (n=123 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Roy-Byrne 2014 (n=868 drug [42% stimulants] using adults in primary care, 1-session MI + booster call vs Control) ○ Woolard 2013 (n=515 alcohol & cannabis using US adults, 2-session in-person MI vs Control) ○ In non-screen detected populations (treatment seeking) (10 trials, MD −0.91, 95% CI −1.52 to −0.31; I^2=86%, p<0.001). ○ Babor 2004 (n=450 cannabis dependent US adults, 9-session MET/CBT vs 2-session MET vs Waitlist) ○ de Dios 2012 (n=34 cannabis using US young adults, 2-session in-person BI vs Control) ○ de Gee 2014 (n=119 cannabis using US adolescents/young adults, 2-session in-person MI vs Control) ○ Fischer 2012 & 2013 (n=134 cannabis using adults, 1-session in-person BI vs Control) ○ Gates 2012 (n=149 cannabis using Australian adolescent/young adults, 4-session phone MI/CBT vs Waitlist) ○ Martin 2008 (n=40 cannabis using Australian adolescents, 2-session in-person MI vs Control)) ○ McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ Rooke 2013 (n=230 cannabis using Australian adults, 6-module web-based MI/CBT vs Control) ○ Schaub 2015 (n=308 cannabis using US adults, 8-module web-based MI/CBT w/ chat vs w/out chat vs Waitlist) ○ Stephens 2000 (n=291 cannabis using US adults, 14-session in-person CBT vs 2-session in-person MI vs Waitlist) ○ **No effect** on drug use in prior 7 days at **6- to 12-month** follow-up (10 trials, MD 0.00, 95% CI −0.24 to 0.22; I^2=42%, p=0.019) ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Blow 2017 (n=780 risky [ASSIST ≥4] drug using US adults in ED, 1-session in-person MI vs 1-session computer MI vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control)	

			○ Lee 2010 (n=341 cannabis using US college age students, 1-session computer-delivered personalized feedback vs Control) ○ Lee 2013 (n=212 cannabis using US college age students, 1-session in-person personalized feedback vs Control) ○ Martino 2018 (n=439 moderate risk [ASSIST 4-26] drug using women primary care reproductive health visit, 1-session in-person BI vs 1-session computer BI vs Control) ○ Paffai 2014 (n=123 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Roy-Byrne 2014 (n=868 drug [42% stimulants] using adults in primary care, 1-session MI + booster call vs Control) ○ Saitz 2014 (RCT, n=528 risky [ASSIST ≥4] drug using [19% cocaine] US adults in primary care, Screening + MI vs Screening + BNI vs Screening alone) ○ Woolard 2013 (n=515 alcohol & cannabis using US adults, 2-session in-person MI vs Control)	
			Brief interventions (1-2 sessions each < 1 hr) for unhealthy drug use vs Other (usually an attentional control, wait-list, or TAU) in **primary care** Includes results for screen-detected and non-screen detected populations • **Higher** drug abstinence rate at 3- to 4-months (10 trials, 244//1413 vs 161/1140, RR 1.47, 95% CI 1.11 to 1.94, p=0.007; I^2=61%, p=0.02) ○ McCambridge 2004; McCambridge 2008; Babor 2004 arm; Bogenschulz 2014; Gelberg 2017, Tzilos Wernette 2018; Ondersma 2007; Ondersma 2014; Ondersma 2018; Zahradnik 2009 • **Higher** drug abstinence rate at 6-12 months (11 trials, 469/2175 vs 336/1746, RR 1.22, 95% CI 1.08 to 1.39, p=0.002; I^2=5%, p=0.39) ○ Baker 2005; Marsden 2006; McCambridge 2004; McCambridge 2008; Bernstein 2005; Bernstein 2009; Bogenschulz 2014; Ondersma 2014; Ondersma 2018; Saitz 2014; Zahradnik 2009 • Drug use days at 3-4 months in (9 trials, MD= −0.13 [−0.36, 0.12]; I^2=42%) • Drug use days at 6-12 months (11 trials, MD= −0.06 [−0.24, 0.11]; I^2=0%)	
Drug use consequences	N/A	Meta-analysis: Tanner-Smith 2022[4] (Supplemental)	**Drug-targeted brief interventions** vs less active comparison condition (eg no treatment, sham, and treatment as usual) in **general medical settings** • **No effect** on drug use consequences (12 RCTs) ○ Individual studies not listed.	

Drug use severity	N/A	Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use vs Other Intervention (control/wait-list/TAU) in primary care**
			• **Lower** drug use severity **at 3-4 months** (17 trials, n=4437, SMD -0.18, 95% CI -0.32 to -0.05; I-squared=73%, p<0.001)
			  ○ Screen-detected populations: **No effect** on drug use severity **at 3-4 months** (9 trials, SMD -0.05, 95% CI -0.15 to 0.05; I^2=17%, p=0.295)
			• **No effect** on drug use severity at **6-12 months** (13 trials, n=3798, SMD -0.1, 95% CI -0.15 to 0.06; I-squared=65%, p=0.001)
			  ○ Screen-detected populations: **No effect** on drug use severity at **6-12 months** (9 trials, SMD -0.03, 95% CI -0.15 to 0.02; I^2=40%, p=0.099)
				USPSTF systematic review of screening in primary care.

			Brief interventions (1-2 sessions each < 1 hr) vs Other (attentional control, wait-list, or TAU) in primary care Including results for screen-detected and non-screen detected populations • Drug use severity at 6-12 months (10 trials, SMD −0.02, 95% CI −0.13 to 0.06)	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Bernstein 2005[5]	RCT 6-mo follow-up USA Primary care	**(1) MI**: One motivational interview session (10-45 min) with a peer interventionist including active referral & referral handout followed in 10 days by one 5-10 min telephone booster call **(2) Control**: Referral handout	N=1175 adults reporting last 30-day cocaine/heroin use (93% cocaine) and DAST10 score ≥ 3 (moderate-to severe problems related to drug use).	**Follow-up**: NSD between groups in follow-up rate (83% vs 81%) **Cocaine abstinence**: Of those cocaine-positive at baseline (n=720), higher abstinence in MI group at follow-up compared to controls (22.3% vs 16.9%, adjusted OR=1.51 [1.01, 2.24, p=0.45). **Cocaine use** (hair sample [ng/10 mg]): Trend for greater reduction in hair levels in MI compared to control group (MD= -29% vs -4%, p=0.058). **Addiction severity** (ASI subscale): Among participants with pre- and post-scores, trend for greater score reduction in MI group (n=962, 49% vs 46%, p=0.06). **Treatment system contact**: NSD among participants abstinent at 6 months (39% vs 37%).	Patnode (2020a)[2] [JAMA] Quality rating: Good Also see EtDT Prev Refer to Tx, EtDT Prev MI-BI

Bogenschutz 2014[6]	RCT 12-mo follow-up USA Emergency Department	(1) **SBIRT**: Screening, assessment, brief intervention, and referral to treatment if indicated with up to 2 telephone boosters (2) **SRT**: Screening, assessment, and referral to treatment if indicated (3) **SO**: Minimal screening only and informational pamphlet	N=1285 adults (30% female, 50% white) with DAST10 score ≥ 3 (moderate-to severe problems related to drug use). Primary substance 27% cocaine, 4% MA, 3% prescription stimulants.	Follow-up rate 81% at 12 months **Cocaine use** (self-report): Among those reporting primary cocaine use (n=349), NSD in number of days using cocaine in past 30 days at the 3-, 6- or 12-month follow-up. **Primary drug use** (hair): Among participants with samples (n= 858), more samples positive for primary drug in the SRT group (95%) compared to SBIRT (89%) or SO group (88%, p=0.02) at 3 months. NSD at other times. **Primary drug use** (self-report): NSD in number of days using primary drug in past 30 days at the 3-, 6- or 12-month follow-up. **Any drug use** (self-report): NSD in number of days using any drug in past 30 days at the 3-, 6- or 12-month follow-up.	
Gelberg 2015[7]	RCT USA Primary care	(1) **SBI**: Screening, brief intervention (median 3-4 mins) with PCP, video, booklet, and up to 2 telephone boosters (20-30 mins each at 2- and 6-wks) with health educators focused on highest scoring illicit drug (HSD)* (2) **Control**: Screening, cancer screening video and pamphlet	N=334 adult (63% male, 38% white) patients with ASSIST score 4-26 (moderately risky drug use indicating physician advice) recruited in FQHC primary care waiting rooms. Excluded in SUD treatment starting more than 30 days ago or pregnant. 32% HSD was stimulants.	Follow-up rate 78% **Riskiest drug use*** (self-report): SBI patients reported using an average of 2.21 fewer days in the previous month than controls (MD= -2.21 [-3.76, -0.65], p=0.005). **Cocaine/crack use** (self-report): SBI patients reported using fewer days in the previous month than controls (n=67, MD=2.77 [-0.08, 5.63]) **MA/ATS use** (self-report): NSD (n=41, MD=0.01 [-7.57, 7.58])	*Initially recruited only stimulant users. Clinicians focused on stimulant use if it scored in the risky range even if it was not the HSD.
Gerdtz 2020[8]	Prospective observation Australia ER	Harm reduction advice and referral	N=457 (59% male) patients admitted to a behavioral assessment unit within an emergency department who tested positive or self-reported amphetamine-type stimulant use	**Referral acceptability:** Most patients accepted a referral to the alcohol and other drug clinician (85.6%, 95% CI 77.2–91.2).	Also see EtDT Prev Refer to Tx
Humeniuk 2012[9]	RCT	**(1) BI**: One 15 min brief intervention	N=731 (USA=218) adolescents and adults (age	85% follow-up rate	Patnode (2020) [AHRQ]

	3 mo Australia, Brazil, India, US Primary care	session based on ASSIST risk score **(2) Waitlist**	16-62) recruited at **primary care** with at least moderate-risk ASSIST score (4-26). Cocaine: 12.9% Amphetamines: 21.2% (44% female)	**Stimulant use** (ASSIST): Overall there was a significantly greater decrease in stimulant-specific substance involvement scores in BI compared to Waitlist groups (5.8 vs 3, F=9.4, p<0.005). However, there was NSD when the analysis was restricted to US participants (4.7 vs 5.3, F=0.08, p=0.8). There was a significant difference for Australian and Brazilian participants (India did not recruit stimulant users).	guideline Quality rating: Fair ITT analysis
Karno 2021[10]	RCT Study period: June 2013 to mid-2017 USA Outpatient (6 sites) & Inpatient (1 site)	**(1) SBIRT:** Single face-to-face session assessment with the ASSIST and BI tailored to ASSIST risk score. **(2) Control**: Health Education session (mean duration 20.3 minutes). **Not detected via universal screening of population.**	N= 718 adults (49.2% female, 47% non-white) seeking mental health treatment with an affective or psychotic disorder diagnosis and reported any use of stimulants, cannabis, or a heavy drinking day in the past 90 days. Excluded if received treatment for a SUD in the previous 90 days. 34.3% reported stimulant use in the prior 90 days. 52.4% of sample exceeded threshold indicating severe mental illness (Kessler-6 score ≥ 13).	**Stimulant abstinence** (self-report): No difference in odds of stimulant abstinence at the 3-, 6- or 12-month follow-up. **Stimulant use frequency** (self-report): Among participants who used stimulants during the follow-up period (n=299), SBIRT participants had fewer days of stimulant use compared to controls at 3-month follow-up (5.8 vs 9.8, OR = 0.58; 95% CI = 0.50 – 0.66). Effects remained at 6-month (4.7 vs 8.9) and 12-month follow-ups (6.1 vs 13.5). **Treatment access:** No difference in utilization of addiction treatment services for receipt of any service within 30 days of intervention (21.3% vs 24.3%) or total number of services received.	Statistical analysis for stimulant sub-group not determined a priori, so results are exploratory only. Also see EtDT Prev Refer to Tx
Marsden 2006[11]	RCT 6 mo follow-up UK Community	**(1) BI**: Self-assessment and single in-person motivational intervention session for 45-60 mins, manual guided, plus printed health risk information **(2) Control:** Self-assessment and printed health-risk information only	N=342 adolescents and young adults aged 16-22 yrs with **problematic** (at least four times over the past month) **MDMA or cocaine** use. Recruited via community advertising, outreach contact, and peer referral.	87.4% follow-up rate. No effect on cannabis or alcohol use. outcomes **Stimulant abstinence** (self-report + saliva testing): NSD. between groups in rate of prior 90-day abstinence from ecstasy, cocaine powder, or crack cocaine at 6-month follow up. **Stimulant use frequency**: NSD between groups in number of ecstasy and crack cocaine use days in previous 90 days at 6 months. Between group contrast for cocaine powder was significant (5.54 vs 7.40, p=0.01) but the effect size was not (d=0.15 [−0.06, 0.37]).	In Li 2016[12] and Patnode (2020a)[2] [JAMA]Quality rating: Good Also see EtDT Adol BI-MI, EtDT Prev MI-BI, EtDT Prev Refer to Tx

				Stimulant use amount: NSD between groups in amount of ecstasy, cocaine powder, or crack cocaine used in previous 90 days at 6 months.	
McCambridge & Strang 2004[13], 2005[14]	Cluster RCT 3, 12 mo follow-up UK Further education colleges	**(1) MI**: Single session (1 hour) in-person adapted from Miller & Rollnick 1991 and Rollnick 1992 **(2) TAU:** Usual education	N=200 adolescents and young adults aged 16-20 yrs with **weekly cannabis use or stimulant use** within the previous 3 months. Recruited by peer interviewers identified by school staff. Baseline stimulant use 23%. **At-risk population.**	89.5% followed up **Stimulant use**: NSD bw groups at 3-month follow-up (24% vs 41%) **Drug-associated problems**: Fewer MI participants reported experiencing problems attributed to the use of stimulants and other drugs (not cannabis, alcohol, tobacco) 3 months after intervention (12% vs 37%, p=0.009) **Readiness to change**: More MI participants reported increasing one motivational stage of change in relation to drug use higher than control group at 3 months after controlling for baseline stage (B = 0.76, p=0.004).	In Li 2016[12] and Patnode (2020a)[2] [JAMA]Quality rating: Fair Also see EtDT Adol BI-MI, EtDT Prev MI-BI, EtDT Prev Refer to Tx
Poblete 2017[15]	RCT 3 month follow-up Chile Primary care, ED, police station	**(1) Brief intervention:** One 18 min in-person brief individual counseling session based on FRAMES. **(2) Control**: Pamphlet	N=806 adults (18-55) with ASSIST score 11 to 20 for alcohol or ASSIST score 4 to 20 for drug use (moderate risk). 19% received a cocaine-related brief intervention	Follow-up rate: 407/8-6 (62%) ASSIS cocaine score, mean (SD): NSD between groups at 3 months (11.1 (9.2) vs 10.3 (8.5), MD=-0.11 (-3.69 to 3.48) ASSIST total score, mean (SD): NSD between groups at 3 months (28.1 (14.4) vs 27.9 (15.0), MD=-0.13 (-1.47 to 1.74)	Patnode 2020 [AHRQ] guideline Also see EtDT Prev SBI & EtDT Prev Refer to Tx
Saitz 2014[16]	RCT June 2009-Jan 2012 6-mo follow-up USA Primary Care	**(1) BNI:** Brief negotiated interview, a 10- to 15-minute structured interview conducted by health educators **(2) MI:** Adaptation of Motivational Interviewing, a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors **(3) No BI:**	N=528 adult with drug use ASSIST substance-specific scores ≥4 at an urban hospital-based primary care internal medicine practice. Baseline 19% reported cocaine as main drug.	**Cocaine use** (hair testing): NSD in % of participants with a positive hair test among participants with a sample (n=199). **Cocaine use amount** (hair testing): NSD in median quantitative level among participants with a sample (n=199). **Cocaine use frequency (self-report**: NSD in number of days of cocaine use in the past 30 days between BNI and Control (IRR=1.51 (0.78-2.91) p=0.31) and MI vs Control (IRR=1.41 (0.73-2.72) p=0.31) among participants with baseline cocaine use (n=97). **Cocaine use severity** (ASSIST): NSD **Drug use consequences**: NSD **Unsafe sex**: NSD **Injection drug use**: NSD	Also see EtDT Prev Refer to Tx

		All participants received a list of SUDr treatment and mutual help resources.		**Mutual help meeting attendance**: NSD **Hospitalizations and ED visits**: NSD **Health care utilization for addiction or mental health reasons**: NSD	
Smout 2010[17]	Pre-post 3-month follow-up Australia Community	**Psychostimulant Check-Up:** Single-session brief intervention for stimulant users	N=80 adults (39% female) who used psychostimulants (**98% injected MA as usual route of administration**) in the previous month recruited though community advertisements and fliers. A majority of participants (55) were in the 'action' stage of readiness to change at baseline.	Follow-up rate 62% **MA use** (self-report): Fewer MA use days at follow up (15 vs 8.3, p<0.001). 25 reported no MA use in prior month at follow-up (28% of follow-up or 16% of baseline sample). 13% reported an increase in monthly consumption. 62% reported at least a 1g reduction in monthly MA use. **MA-related negative consequences** (self-report): Fewer experienced in the previous month at follow up (85 vs 59.5, p=0.002). **Injection use** (self-report): Fewer reported injection as the usual route of administration at follow up (n=11, 78% vs 55%, p=0.004). **Readiness to change**: No change in proportion of participants in each stage **Treatment engagement**: NSD in number of health service contacts in last month (2 vs 1.9, p=0.813) **Patient satisfaction**: 90% responding they were very satisfied or mostly satisfied with the Check-Up. 66% said it answered their questions, 92% increased awareness of services, and 91% would recommend it to friends.	Also see EtDT Prev IDU Counseling, EtDT Prev MI-BI, EtDT Prev Refer to Tx

Existing Guidelines

Substance Abuse and Mental Health Services Administration. TIP 33: Treatment for Stimulant Use Disorders. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Unhealthy Drug Use: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;323(22):2301. doi:10.1001/jama.2020.8020

Grigg J, Manning V, Arunogiri S, et al. Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals. 2nd ed. Turning Point; 2018.

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.d

Department of Veterans Affairs (VA), Department of Defense (DoD). VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Management of Substance Use Disorders Work Group. Department of Veteran Affairs & Department of Defense; 2016. https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf

World Health Organization. Technical Brief 4 on Amphetamine-Type Stimulants (ATS): Therapeutic interventions for Users of Amphetamine-Type Stimulants (ATS).; 2011.

Patnode CD, Perdue LA, Rushkin M, O'Connor EA. *Screening for Unhealthy Drug Use in Primary Care in Adolescents and Adults, Including Pregnant Persons: Updated Systematic Review for the U.S. Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2020. Accessed April 29, 2022. http://www.ncbi.nlm.nih.gov/books/NBK558174/

Resources from Existing Guidelines

Source	Resource	Comments
	Finding Quality Treatment for Substance Use Disorders (https://store.samhsa.gov/product/ PEP18-TREATMENT-LOC): This resource is for people seeking behavioral health services and treatment for SUDs. It provides guidance on how to find a quality treatment center and the steps to complete before accessing treatment.	
	TIP 35: Enhancing Motivation for Change in Substance Use Disorder Treatment (https:// store.samhsa.gov/product/PEP19-02-01-003): TIP 35 describes the elements of motivational interventions, the five principles of MI, catalysts for changing behavior, and the stages of change that clients go through while working toward recovery from SUDs	
	Substance Abuse and Mental Health Services Administration. (2011). Screening, brief intervention and referral to treatment (SBIRT) in behavioral healthcare. Substance Abuse and Mental Health Services Administration.	
Smout 2008	Smout M, Krasnikow S, Longo M, Wickes W, Minniti R, Cahill S. Quickfix: Identity & Intervene in Psychostimulant Use in Primary Health Care (Updated 2015). Drug and Alcohol Services South Australia; 2008. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/quickfix+identity+intervene+in+psychostimulant+use+in+primary+health+care	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence that brief intervention reduces stimulant use in adolescents and YAs based on a MA of 4 RCTs and 1 RCT (Saitz 2014)[15]. However, there is evidence that screening and brief intervention reduces use of a broader category of substances other than alcohol. Effect sizes ranged … 1 RCT found a 1-hour counseling session increased readiness to change their cannabis or stimulant use, but it is not known if the intervention was directed at referral to treatment. NSD in treatment system contact in other RCTs. It is possible that the impact of referral to treatment is diluted by the relatively low prevalence of StUD and need for treatment in the study populations.	Brief intervention is a necessary first step to providing non-SBI harm reduction education and treatment for stimulant use, which can lead to other outcomes including reduction of harms stemming from use, increasing readiness to change, and increasing motivation for treatment. The benefits of offering treatment to those who need it is substantial, although this population will be small. Benefits will depend on patient readiness.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients may be upset to be invited to discuss their substance use. Patients may be uncomfortable receiving a referral to treatment.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	The benefits of engaging the patients in treatment is possibly significant and outweighs the risk of straining the therapeutic alliance, but depends on patient readiness.	☐ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☒ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
MA and SR interventions blended RT and clinical interventions where the goal was treatment entry (ie, extended duration sessions, multiple session interventions)	Drawing from substance use reduction and other outcomes not covered in the literature review.	☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Is there existing inequity in referral? There is in availability of good places to refer people to.	Depends on implementation. If done equitably could reduce, if done poorly could increase.	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Gerdtz 2020[8] found referrals were acceptable by patients.	Referral incurs a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Referral incurs a short-term time cost for clinicians. This cost will vary by clinician and setting. Clinicians must be knowledgeable and up to date regarding local treatment options. The differences between busy EDs, primary care offices, and outpatient settings in terms of available time and clinical ability may determine whether the clinician conducts or needs to refer patients for a full assessment.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusions

Justification

Brief intervention is a necessary first step to providing non-SBI harm reduction education and treatment for stimulant use, which can lead to other outcomes including reduction of harms stemming from use, increasing readiness to change, and increasing motivation for treatment.

Subgroup Considerations

- Rural areas have high prevalence and high barriers. Consider telemedicine referral.
- Effectiveness depends on patient readiness for change

Implementation Considerations

- There are situations where stimulant intox/wd is not associated w/ StUD (a.k.a. use does not = use disorder), so assessment is still required.
- Timing of intervention is a functional determination on the basis of behavior. Do it multiple times is better than waiting.

Research Priorities

- Feasibility research – peer navigation, telemedicine, use of technology to improve warm handoff/linkage to treatment, cost effectiveness

References

1. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
2. Patnode CD, Perdue LA, Rushkin M, et al. Screening for Unhealthy Drug Use: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;323(22):2310. doi:10.1001/jama.2019.21381
3. Sayegh CS, Huey SJ, Zara EJ, Jhaveri K. Follow-up treatment effects of contingency management and motivational interviewing on substance use: A meta-analysis. *Psychol Addict Behav*. 2017;31(4):403-414. doi:10/gbjxgb
4. Tanner-Smith EE, Parr NJ, Schweer-Collins M, Saitz R. Effects of brief substance use interventions delivered in general medical settings: a systematic review and meta-analysis. *Addict Abingdon Engl*. 2022;117(4):877-889. doi:10.1111/add.15674
5. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend*. 2005;77(1):49-59. doi:10.1016/j.drugalcdep.2004.07.006

6. Bogenschutz MP, Donovan DM, Mandler RN, et al. Brief Intervention for Patients With Problematic Drug Use Presenting in Emergency Departments: A Randomized Clinical Trial. *JAMA Intern Med*. 2014;174(11):1736-1745. doi:10.1001/jamainternmed.2014.4052
7. Gelberg L, Andersen RM, Afifi AA, et al. Project QUIT (Quit Using Drugs Intervention Trial): A randomized controlled trial of a primary care-based multi-component brief intervention to reduce risky drug use. *Addict Abingdon Engl*. 2015;110(11):1777-1790. doi:10.1111/add.12993
8. Gerdtz M, Yap CYL, Daniel C, et al. Amphetamine-type stimulant use among patients admitted to the emergency department behavioural assessment unit: Screening and referral outcomes. *Int J Ment Health Nurs*. 2020;29(5):796-807. doi:10/gn756q
9. Humeniuk R, Ali R, Babor T, et al. A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries: Brief intervention for illicit drugs. *Addiction*. 2012;107(5):957-966. doi:10.1111/j.1360-0443.2011.03740.x
10. Karno MP, Rawson R, Rogers B, et al. Effect of screening, brief intervention and referral to treatment for unhealthy alcohol and other drug use in mental health treatment settings: a randomized controlled trial. *Addict Abingdon Engl*. 2021;116(1):159-169. doi:10/gn756x
11. Marsden J, Stillwell G, Barlow H, et al. An evaluation of a brief motivational intervention among young ecstasy and cocaine users: no effect on substance and alcohol use outcomes. *Addiction*. 2006;101(7):1014-1026. doi:10.1111/j.1360-0443.2006.01290.x
12. Li L, Zhu S, Tse N, Tse S, Wong P. Effectiveness of motivational interviewing to reduce illicit drug use in adolescents: a systematic review and meta-analysis. *Addiction*. 2016;111(5):795-805. doi:10.1111/add.13285
13. McCambridge J, Strang J. The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial. *Addiction*. 2004;99(1):39-52. doi:10.1111/j.1360-0443.2004.00564.x
14. McCambridge J, Strang J. Deterioration over time in effect of Motivational Interviewing in reducing drug consumption and related risk among young people. *Addiction*. 2005;100(4):470-478. doi:10.1111/j.1360-0443.2005.01013.x
15. Poblete F, Barticevic NA, Zuzulich MS, et al. A randomized controlled trial of a brief intervention for alcohol and drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in primary health care in Chile: ASSIST-BI for alcohol and drugs in Chile. *Addiction*. 2017;112(8):1462-1469. doi:10.1111/add.13808
16. Saitz R, Palfai TPA, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513. doi:10.1001/jama.2014.7862
17. Smout M, Longo M, Harrison S, et al. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. *Drug Alcohol Rev*. 2010;29(2):169-176. doi:10.1111/j.1465-3362.2009.00133.x

Secondary and Tertiary Prevention

Screening

Table 47. Screening for Stimulants

Recommendation: When general healthcare providers screen adolescents or adults for risky substance use per USPSTF guidelines, they should include screening for stimulant misuse (ie, non-medical or non-prescribed use).

Clinical Question Summary Table

Clinical Question	1. What Is the accuracy of drug use screening Instruments for risky stimulant use? 2. Does screening for stimulant use reduce stimulant use or improve other risky behaviors? 3. What are the harms of screening for risky stimulant use?
Population	Adolescent and adult patients
Intervention	Screening for risky stimulant use with frequency-based and risk assessment tools
Comparison	Don't screen
Main Outcomes	Stimulant use, risky behavior, harms of screening, identification of risky stimulant use
Setting	General clinical (medical, psychiatric) settings
Background & Definitions	Screening refers to asking questions about drug use or related risks, not toxicology testing.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Tools

NIDA Quick Screen
NIDA 1-item screen (Saitz)
NIDA-Modified ASSIST
ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) 1. In your life, which of the following substances have you ever used? 2. In the past 3 months, how often have you used the substances you mentioned? 3. During the past 3 months, how often have you had a strong desire or urge to use the substance? 4. During the past 3 months, how often has your use of the substance led to health, social, legal, or financial problems? 5. During the past 3 months, how often have you failed to do what was normally expected of you because of your use of the substance? 6. Has a friend or relative or anyone else ever

expressed concern about your use? 7. Have you ever tried and failed to control, cut down, or stop using? 8. Have you ever used any drug by injection? (Includes opening question to assess use)
ASSIST-Lite In the past 3 months: 1 Did you smoke a cigarette containing tobacco? 2 Did you have a drink containing alcohol? 3 Did you use cannabis? 4 Did you use an amphetamine-type stimulant, or cocaine, or a stimulant? 4a Did you use a stimulant at least once each week or more often? Yes [1] No [0] 4b Has anyone expressed concern about your use of a stimulant? 5 Did you use a sedative or sleeping medication not as prescribed? 6 Did you use a street opioid (eg heroin), or an opioid-containing medication not as prescribed? 7. Did you use any other psychoactive altering substance?
DIPS (Depression, Insomnia, Psychotic symptoms, Scabs) Psychostimulant use in primary care (Smout et al., 2008)
TAPS-1 (Tobacco, Alcohol, Prescription Medication, and Other Substance use – rapid screener) In the past 12 months, how often have you: 1. Used any tobacco product (for example, cigarettes, e-cigarettes, cigars, pipes, or smokeless tobacco)? 2. Had 5/4 (M/F) or more drinks containing alcohol in one day? 3. Used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy (MDMA)? 4. Used any prescription medications just for the feeling, more than prescribed, or that were not prescribed for you? (Prescription medications that may be used in this way include: opioid pain relievers (eg, Oxycontin, Vicodin, Percocet, methadone), medications for anxiety or sleeping (eg, Xanax, Ativan, Klonopin), medications for ADHD (eg, Adderall or Ritalin)
Alcohol HED (Heavy episodic drinking) 1. How many times in the past year have you had 5/4 (male/female) or more drinks in a day? (Often includes opening question to assess use)
SoDU (Screen of Drug Use; Tiet et al., 2015) 1. How many days in the past 12 months have you used drugs other than alcohol? 2. How many days in the past 12 months have you used drugs more than you meant to?
SDS (Severity of Dependence Scale; Gosson, 1995; range of 0–15 points, higher is worse) In the past X months, how often (0 = never/almost never; 1 = sometimes; 2 = often; 3 = always/nearly always) (1) Did you think your use of (named drug) was out of control? (2) Did the prospect of missing a hit (line, dose) of (named drug) make you anxious or worried? (3) Did you worry about your use of (named drug)? (4) Did you wish you could stop to use (named drug)? (5) How difficult would you find it to stop or go without (named drug)? (0 = not difficult; 1 = quite difficult; 2 = very difficult; 3 = impossible)

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Outcome Importance	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Identification of risky stimulant use	N/A	N/A	Meta-analysis: Patnode 2020 JAMA[1] AHRQ[2] (Supplementary)	Performance of frequency-based and risk assessment tools to identify: **Cocaine use**: Sensitivity 70-95%, Specificity 80-88% (2 studies, n=43,322) • Dawson 2010 (n=42,923 Community, Alcohol HED); Kumar 2016 (n=399 Primary Care, CA ASSIST) **Unhealthy cocaine/MA use**: Sensitivity 64-80%, Specificity 98-99% (1 study, n=1995) • McNeely 2016 (n=1995 Primary Care, TAPS) **Cocaine/MA use disorder** (abuse/dependence): Sensitivity 47-98%, Specificity 83-100% (3 studies, n=45,317) • Dawson 2010 (n=42,923 Community, Alcohol HED); Kumar 2016 (n=399 Primary Care, CA ASSIST); McNeely 2016 (n=1995 Primary Care, TAPS)	USPSTF systematic review of screening in primary care

				"The low prevalence of prescription drug misuse and other drug types (cocaine, heroin) also leads to poor precision in some estimates." (Patnode et al., 2020, p. 41)	
Drug screening accuracy	N/A	N/A	Meta-analysis: Patnode 2020 JAMA[1] (Supplementary)	Performance of frequency-based and risk assessment tools to identify: **Drug use**: Sensitivity 73-93%, Specificity 86-96% (2 studies, n=745) • McNeely 2015 (n=459 1-item drug frequency); Smith 2010 (n=286 1-item drug frequency, DAST-10) **Unhealthy drug use**: Sensitivity 71-94%, Specificity 87-97% (3 studies, n=1512) • McNeely 2015 (n=586 1-item drug frequency, SUBS); Smith 2010 (n=286 1-item drug frequency, DAST-10); Tiet 2015 (n=640 ASSIST-Drug, DAST-2, SoDU) **Drug use disorder** (abuse/dependence): Sensitivity 85-100%, Specificity 67-93% (4 studies, n=1651) • McCann 2000 (n=139 ADHD clinic, DAST-28); McNeely 2015 (n=586 1-item drug frequency, SUBS); Smith 2010 (n=286 1-item drug frequency, DAST-10); Tiet 2015 (n=640 ASSIST-Drug, DAST-2, SoDU)	USPSTF systematic review of screening in primary care
Benefits of screening	N/A	N/A	Systematic review: Patnode 2020 AHRQ[2] (Supplementary)	No trials found that addressed the effect of screening alone (ie, with no BI) on reduced drug use or risky behavior (Patnode et al., 2020, p. 5).	USPSTF systematic review of screening in primary care
Harms of screening	N/A	N/A	Systematic review: Patnode 2020 AHRQ[2] (Supplementary)	No evidence found that addressed the harms of screening alone (ie, with no BI) for drug use (Patnode et al., 2020, p. 5),	USPSTF systematic review of screening in primary care

Individual studies reporting screen performance results for stimulants

Study	Screen	Cut-Off (score)	Prevalence in Sample (%)	Sensitivity (95% CI)	Specificity (95% CI)	AUC
Ali 2013[3]	ASSIST-Lite	Stimulant use disorder (2)		0.96 (0.93, 0.99)	0.71 (0.57, 0.86)	0.85
Tiet & Moos 2021[4]	SoDU	Cocaine/amphetamine use disorder (1)	6.2	93.67 (85.84, 97.91)	89.12 (87.22, 90.82)	0.91
		Cocaine use disorder (1)	3.3	95.24 [83.81–99.42]	86.70 (84.69, 88.54)	0.91

		Amphetamine use disorder (1)	3.9	94 (83.45–98.75	87.19 (85.19, 89)	0.91
Dawson 2010[5]	Alcohol HED	Cocaine use in past year (1)	0.5	77.6 (71.4, 82.5)	84.5 (84.2, 84.8)	0.893
		Cocaine abuse (7)	0.2	76.0 (66.9, 83.6)	84.3 (84, 84.6)	0.897
		Cocaine use disorder (12)	0.1	76.0 (61.9, 85.4)	86.0 (85.7, 86.3)	0.887
Kumar 2016[6]	CA ASSIST	Cocaine use in past year (2)	9.0	86 (70, 95)	84 (80, 88)	0.85
		Cocaine use disorder (4)	7.3	90 (73, 98)	97 (83, 90)	0.88
McNeely 2016[7]	TAPS	Cocaine/MA unhealthy use (1) interviewer delivered	6.0	68 (59, 77)	99 (98, 99)	
		Cocaine/MA unhealthy use (1) self-administered	6.0	73 (64, 80)	99 (98, 99)	
		Cocaine/MA use disorder (2) interviewer delivered	5.4	57 (47, 67)	99 (99, 100)	
		Cocaine/MA use disorder (2) (self-administered)	5.4	60 (50, 69)	99 (99, 99)	

Screening studies reporting results for stimulants: Study characteristics

Study	Screen	Reference standard	Participants	Outcomes	Comments
Ali 2013[3]	**ASSIST-Lite:** Short form of the Alcohol, Smoking and Substance Involvement Screening Test Screen type: Risk assessment	MINI-Plus DSM-IV	N=2,082 adults recruited from general medical (70%) and specialist mental health/addiction treatment services (22%) in 9 countries. 571 (28%) reported using stimulants in the past 3 months.	See table Two items (weekly or more often consumption and anyone expressing concern about use) had high diagnostic accuracy for stimulants. No significant test bias for gender, age, setting or country was found.	Subjects from specialty settings had higher levels of use overall
Dawson 2010[5]	**Alcohol HED:** Single-item screen for heavy episodic drinking (HED) Screen type: Indirect	NESARC (National Epidemiologic Survey on Alcohol and Related Conditions)	N= 42,923 adults recruited from the community. Country: USA	See table	Patnode 2020 [AHRQ] guideline: Fair quality
González-Sáiz 2009[8]	**SDS:** Severity of Dependence scale, cut off score 4 for current cocaine dependence	PRISM (Psychiatric Research Interview for Substance and Mental Disorders)	N=135 young (18–30 years old) current heroin and cocaine users, 51% with current cocaine use	AUC for CoUD 0.85 (95% CI 0.78–0.92), suggesting a high diagnostic utility for cocaine dependence.	

		using DSM-IV criteria	disorder (CoUD) as determined by the PRSM DSM-IV. 2001 and 2003 Country: Spain Setting: Community	Using a cut off score 4 for current cocaine dependence. - Sensitivity 79.7% - Specificity 86.4% - PPV 85.9 - NPV 80.4	
Kaye 2002[9]	**SDS:** Severity of Dependence scale, cut off score 3	CIDI (Composite International Diagnostic Interview) using DSM-IV criteria	N=142 cocaine users (23% of them in methadone maintenance treatment)	Cocaine dependence ROC 0.86 Sensitivity 67% Specificity 93%	
Kumar 2016[6]	**CA ASSIST:** Audio Computer Assisted Self Interview version of the ASSIST Screen type: Risk assessment	MINI Plus	N= 399 adults recruited consecutively from an urban safety-net primary care clinic. White: 19.8 Black: 47.9 Country: USA Setting: Primary care	See table	Patnode 2020 [AHRQ] guideline: Good quality Not enough data to evaluate for prescription stimulants or methamphetamine
McNeely 2016[7]	**TAPS:** Tobacco, Alcohol, Prescription Medication, and Other Substance use) Screen type: Frequency-based	CIDI (Composite International Diagnostic Interview)	N=1995 adults recruited from primary care. White: 33.4% Black: 55.6% Country: USA Setting: Primary care	See table	Patnode 2020 [AHRQ] guideline: Fair quality
Serowik 2021[10]	**Provider detection**: Any documented SUD in the EHR by any provider (not just study-participating providers), using hospital billing and problem list codes during the hospitalization or within available discharge summaries. **Diagnosis, not a screen**	MINI DSM-5	N= 1076 (586, 55% male) adults with a diagnosis of nicotine, alcohol, or illicit drug use disorder as determined by the MINI DSM-5 receiving inpatient care on one of 13 general medical units at a large urban teaching hospital and expected length of stay ≥2-3 days. Recruited from a cluster RCT of SBIRT. (Clinical Trials.gov: NCT01825057). 131 (12.2%) participants had cocaine use disorder (CoUD) as determined by the MINI DSM-5.	**CoUD sensitivity**: Providers detected 61% of the 131 patients with CoUD. **CoUD specificity**: 93% **CoUD accuracy**: 89% **Health equity**: Odds of provider detection of cocaine use disorder (n=131) lower for Hispanic compared to White patients (OR 0.26, 95% CI 0.07-0.92, p<0.05).	

			Country: USA Setting: Hospital inpatient		
Tiet & Moos 2021[4]	**SoDU** (Screen of Drug Use) to screen for stimulant use disorder Screen type: Risk assessment	MINI DSM-IV	N=1283 VA primary care patients (95% male), 79 (6.2%) met criteria for a stimulant use disorder (cocaine and/or amphetamine use disorder) as determined by the MINI DSM-IV. Retrospective chart analysis Country: USA Setting: Primary care	See table **SoDU + 1:** With follow up question added ("Did you use stimulants more than once in the past 12 months to get high, to feel better, or to change your mood?") - **Specificity** increased for StUD 98.84, CoUD 98.95, and ATStUD 98.70 - S**ensitivity** did not change for StUD, CoUD, or ATStUD **Patient subgroups:** - **StUD sensitivity**: Lowest for older adults (66%), but ranged 91-100% for other subgroups. - **StUD specificity**: Lowest for PTSD (77%), but ranged 83-94% for other subgroups (gender, age, ethnicity, education, PTSD).	"The SoDU, especially with a follow-up question, is an appropriate instrument for routine screening of stimulant use disorder in VA primary care settings. It has good concurrent diagnostic validity for diverse groups of patients."
Topp 1997[11]	**SDS:** Severity of Dependence scale, cut off score 4	CIDI (Composite International Diagnostic Interview) using DSM-III-R criteria	N=327 regular users of amphetamines, 64% with ATS dependence according to the CIDI.	Amphetamines ROC 0.82 Sensitivity 71.3% Specificity 77.1%	

CIDI: Composite International Diagnostic Interview

MINI: Multi International Neuropsychiatric Interview, a semi-structured diagnostic interview using DSM criteria. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

PRISM: Psychiatric Research Interview for Substance and Mental Disorders using DSM criteria. Hasin D, Samet S, Nunes E, Meydan J, Matseoane K, Waxman R: Diagnosis of comorbid psychiatric disorders in substance users assessed with the Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV. Am J Psychiatry 2006;163:689696.

Evidence-Based Guidelines

US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Unhealthy Drug Use: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(22):2301. doi:10.1001/jama.2020.8020

Department of Veterans Affairs (VA), Department of Defense (DoD). VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Management of Substance Use Disorders Work Group. Department of Veteran Affairs & Department of Defense; 2016. https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

National Institute for Health and Care Excellence. *Violence and Aggression: Short-Term Management in Mental Health, Health and Community Settings*. Guideline NG10. National Institute for Health and Care Excellence (NICE); 2015.

Patnode CD, Perdue LA, Rushkin M, O'Connor EA. *Screening for Unhealthy Drug Use in Primary Care in Adolescents and Adults, Including Pregnant Persons: Updated Systematic Review for the U.S. Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2020. Accessed April 29, 2022. http://www.ncbi.nlm.nih.gov/books/NBK558174/

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Stimulant misuse (ie, non-medical or non-prescribed use) can be identified using existing screening instruments. No direct benefits of screening alone were observed.	Screening is a necessary prior step to conducting a further assessment for risky stimulant use.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients may be upset to be asked about their substance use.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	The benefits of identifying who needs subsequent assessment, BI, or treatment is significant and outweighs the risk of straining the therapeutic alliance.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment ☒ Very low ☐ Low ☐ Moderate ☐ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Some patients do not wish to discuss substance use	☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Universal screening should reduce health inequities	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

The recommendation to screen for stimulant misuse follows from the USPSTF recommendation.

Subgroup Considerations

None noted

Implementation Considerations

- Use an existing screening instrument that includes the use of stimulants. Not every screening tool does.
- Typical thresholds for "good" sensitivity and specificity given the population prevalence of stimulant use

References

1. Patnode CD, Perdue LA, Rushkin M, et al. Screening for Unhealthy Drug Use: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;323(22):2310. doi:10.1001/jama.2019.21381
2. Patnode CD, Perdue LA, Rushkin M, O'Connor EA. *Screening for Unhealthy Drug Use in Primary Care in Adolescents and Adults, Including Pregnant Persons: Updated Systematic Review for the U.S. Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2020. Accessed April 29, 2022. http://www.ncbi.nlm.nih.gov/books/NBK558174/
3. Ali R, Meena S, Eastwood B, Richards I, Marsden J. Ultra-rapid screening for substance-use disorders: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite). *Drug Alcohol Depend*. 2013;132(1-2):352-361. doi:10.1016/j.drugalcdep.2013.03.001
4. Tiet QQ, Moos RH. Screen of drug use: Diagnostic accuracy for stimulant use disorder. *Addict Behav*. 2021;112:106614. doi:10/gn758b
5. Dawson DA, Pulay AJ, Grant BF. A Comparison of Two Single-Item Screeners for Hazardous Drinking and Alcohol Use Disorder. *Alcohol Clin Exp Res*. 2010;34(2):364-374. doi:10.1111/j.1530-0277.2009.01098.x
6. Kumar PC, Cleland CM, Gourevitch MN, et al. Accuracy of the Audio Computer Assisted Self Interview version of the Alcohol, Smoking and Substance Involvement Screening Test (ACASI ASSIST) for identifying unhealthy substance use and substance use disorders in primary care patients. *Drug Alcohol Depend*. 2016;165:38-44. doi:10.1016/j.drugalcdep.2016.05.030
7. McNeely J, Wu LT, Subramaniam G, et al. Performance of the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool for substance use screening in primary care patients. *Ann Intern Med*. 2016;165(10):690-699. doi:10.7326/M16-0317
8. González-Saiz F, Ballesta Gomez R, Acedos Bilbao I, Lozano Rojas OM, Gutiérrez Ortega J. Methadone-treated patients after switching to buprenorphine in residential therapeutic communities: An addiction-specific assessment of quality of life. *Heroin Addict. Relat. Clin. Probl.* 2009;11(2):9-19.
9. Kaye S, Darke S. Determining a diagnostic cut-off on the Severity of Dependence Scale (SDS) for cocaine dependence. *Addiction.* 2002;97(6):727-731.
10. Serowik KL, Yonkers KA, Gilstad-Hayden K, Forray A, Zimbrean P, Martino S. Substance Use Disorder Detection Rates Among Providers of General Medical Inpatients. *J Gen Intern Med*. 2021;36(3):668-675. doi:10.1007/s11606-020-06319-7
11. Topp L, Mattick RP. Choosing a cut-off on the Severity of Dependence Scale (SDS) for amphetamine users. *Addiction.* 1997;92(7):839-845.
12. Smout M, Krasnikow S, Longo M, Wickes W, Minniti R, Cahill S. Quickfix: Identity & Intervene in Psychostimulant Use in Primary Health Care (Updated 2015). Drug and Alcohol Services South Australia; 2008. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/quickfix+identity+intervene+in+psychostimulant+use+in+primary+health+care

Table 48. Screening for Prescription Psychostimulants

Recommendation: Clinicians should consider more frequent screening for stimulant misuse in patients who take prescribed psychostimulant medication.

Clinical Question Summary Table

Clinical Question	Should clinicians consider more frequent screening for stimulant use in patients who take prescribed psychostimulant medication?
Population	Patients who take prescribed psychostimulant medication
Intervention	More frequent screening
Comparison	TAU (no screening)
Main Outcomes	Stimulant use outcomes
Setting	Outpatient settings
Background & Definitions	There is evidence that taking a psychostimulant as prescribed does not increase the risk of developing a stimulant use disorder, and that early and intense treatment of ADHD with stimulant medication may even have protective effects.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No research was identified.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Limited evidence on frequency of screening for the general population. Rates of misuse Depend on setting?	Positive screen can indicate need for counseling and prevent non-prescription stimulant use.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Assuming appropriate follow-up intervention is undertaken.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	In general medical settings substantial given no downside.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No evidence ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Minimize harm and maximize benefit	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		

Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

While there is limited evidence for more frequent screening, it is advantageous to identify issues of substance misuseas early as possible

Subgroup Considerations

No other subgroup considerations noted

Implementation Considerations

Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.

Table 49. Check Prescription Drug Monitoring Program

Recommendation: Clinicians should check their state's Prescription Drug Monitoring Program (PDMP) prior to prescribing psychostimulant medication.

Clinical Question Summary Table

Clinical Question	Should clinicians always check their state's PDMP prior to prescribing psychostimulant medication?
Population	Individual or population level?
Intervention	Check PDMP routinely
Comparison	Not checking
Main Outcomes	Decreased overdose risk (long-term)
Setting	Outpatient
Background & Definitions	Background information on the question, more detailed description of the interventions Notes • PDMPs were not associated with a decrease in overall overdose mortality rate or in prescription opioid overdose mortality rate. PDMP operation was also not associated with decreased psychostimulant-involved drug overdose mortality. In fact, PDMPs were associated with increased overdose mortality rate, including cocaine-associated overdose mortality, in states where PDMPs have been in operation for longer periods of time, although this was not consistent across data sets (Nam 2017)[1]. • PDMP's role in prescribing surveillance: "Few studies have investigated stimulants and gabapentin prescribing [34■,54■]." (Delcher 2020, p4)[2] Friedman 2019: "This study examined differential opioid, benzodiazepine, and stimulant prescribing by race/ethnicity and income class in California. Across all drug categories, controlled medications were much more likely to be prescribed to individuals living in majority-white areas." (Delcher 2020, p10)[2]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/ Important Outcomes				

Overdose deaths	N/A	Systematic review: Haegerich 2019[3] (Not assessed)	"stronger PDMP states, such as those that required mandatory use, monitored more than schedule II drugs, and updated more frequently (eg, daily), demonstrated greater reductions in overdose deaths involving prescription opioids (Pardo, 2016)." (p. 5) "Of the three studies that examined impact on overdose, two found no significant changes or differences in drug or opioid overdose mortality (Nam et al., 2017; Paulozzi et al., 2011). Yet, one found significantly lower opioid-related death rates in states with a PDMP compared to those without, particularly when the PDMP was more robust in terms of number of drug schedules monitored, mandated use, and update frequency (Patrick et al., 2016); estimating there could have been 600 fewer opioid overdose deaths in 2016 if Missouri adopted a PDMP and other states enhanced their programs. In two studies examining treatment admissions in PDMP states compared to non-PDMP states, one study found a significant decrease in PDMP states (Simeone and Holland, 2006) while the other did not (Reifler et al., 2012)." (p. 5)	Opioid focus
SUD treatment referral	N/A	Systematic review: Picco 2021[4] (Not assessed)	Identified 39 studies on the effect of PDMPs on prescribing decision making. Study designs: 1 Prospective controlled experiment, 2 pre-post survey, 1 prospective observational, 1 prospective quasi-experimental, 21 cross-sectional survey, 11 qualitative, and 2 mixed methods. Five studies (all cross-sectional surveys) reported that PDMP use resulted in referrals to substance abuse treatment (Goodin et al., 2021; Green et al., 2012, 2013; Rickles et al., 2021; Young et al., 2017).	How prescription drug monitoring programs influence clinical decision-making
Education and counseling	N/A	Systematic review: Picco 2021[4] (Not assessed)	Eight studies (5 cross-sectional surveys, 3 qualitative) reported that PDMP use resulted in the clinical decision to provide patient education and or counselling following PDMP utilization (Finley et al., 2018; Green et al., 2012, 2013; Hernandez-Meier et al., 2017; Rickles et al., 2021; Rittenhouse et al., 2015; Smith et al., 2015; Thornton et al., 2020)	How prescription drug monitoring programs influence clinical decision-making

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention/Comparator	Participants	Outcomes			Comments
Sood 2019[5]	Prospective chart review	(1) Arizona's PDMP (2) Clinical history & urine drug screen (UDS) obtained	N=127 patients with substance use disorder admitted to inpatient	Rx SUD	PDMP	H&UDS	Author conclusion: PDMP is not useful
				Identified	10	67	
				Missed	59	2	

	USA Mental health hospital	during the initial evaluations at intake	behavioral health units for psychiatric care in a 30-day period. 69 (54%) of patients had a prescription substance use disorder (opiate, benzodiazepine or amphetamine).	History and UDS identified 125 (98.4%) of all substance users (n=127), while 1.6% were missed and identified exclusively by using the PDMP. PDMP identified 14% of the prescription substance users (n=69), while history and UDS identified all of them.	for detecting substance abuse.

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
One systematic review found that the effect of PDMPs did on opioid overdose rates was varied. It did change prescriber behavior.	While the evidence is weak, clinical experience suggests that the information gained by checking the PDMP can lead to large benefits in patient safety and indicating the need for patient education and/or treatment.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Clinicians may misinterpret the PDMP and use it punitively. It is difficult to judge the magnitude of undesirable effects for appropriate prescribing, especially in the context of opioids, as the "correct" population prescribing rate is unknown. It is difficult to judge the magnitude of undesirable effects from initiating a conversation about a patient's prescription as self-reported misinterpretation of the PDMP is likely to be underreported.	☐ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	The likelihood of clinicians misusing the PDMP can be reduced through education, which does not suggest the intervention should not be implemented.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Clinical judgment is high, but research evidence is variable.	☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Universally checking PDMP would reduce inequities	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Varies by state program, but in most situations should be easy.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusions

Justification

While the evidence is weak, clinical experience suggests that the information gained by checking the PDMP can lead to large benefits in patient safety and indicate the need for patient education and/or treatment interventions

Subgroup Considerations

None noted

Implementation Considerations

Proper interpretation of the PDMP.

References

1. Nam YH, Shea DG, Shi Y, Moran JR. State Prescription Drug Monitoring Programs and Fatal Drug Overdoses. *Am J Manag Care*. 2017;23(5):297-303.
2. Delcher C, Pauly N, Moyo P. Advances in prescription drug monitoring program research: a literature synthesis (June 2018 to December 2019). *Curr Opin Psychiatry*. 2020;33(4):326-333. doi:10.1097/YCO.0000000000000608
3. Haegerich TM, Jones CM, Cote PO, Robinson A, Ross L. Evidence for state, community and systems-level prevention strategies to address the opioid crisis. *Drug Alcohol Depend*. 2019;204:107563. doi:10.1016/j.drugalcdep.2019.107563
4. Picco L, Lam T, Haines S, Nielsen S. How prescription drug monitoring programs influence clinical decision-making: A mixed methods systematic review and meta-analysis. *Drug Alcohol Depend*. 2021;228:109090. doi:10.1016/j.drugalcdep.2021.109090
5. Sood S, Cowdrey A, Bhattarai B, et al. Prescription Drug Monitoring Programs: Does the Arizona CSPMP Provide More Information than Routinely Collected in an Inpatient Psychiatric Facility? *Subst Use Misuse*. 2019;54(1):106-109. doi:10.1080/10826084.2018.1504082

Assessment

Table 50. Assess Route Complications - Prevention

Recommendation: For patients who screen positive for stimulant misuse:

a. Clinicians should conduct a focused history and clinical exam to evaluate complications of use related to route of administration and type of preparation used and provide treatment or referrals as appropriate.
b. Clinicians should assess the following to determine harm reduction service and counseling needs:
    i. Routes of administration, particularly injection drug use.

Clinical Question Summary Table

Clinical Question	What are effective strategies for assessing route of administration and related history of complications?
Population	Patients who screen positive for stimulant misuse
Intervention	Strategies for assessing route of administration and related history of complications
Comparison	TAU (not addressed)
Main Outcomes	Health outcomes
Setting	Outpatient settings
Background & Definitions	Background information on the question, more detailed description of the interventions Notes: • MA-dependent adults (N = 301) interviewed and examined 3 years after treatment. Among the most frequently reported lifetime conditions were wounds and burns (40.5%, N = 122) (Mooney 2019) • "The potential negative health consequences associated with the use of stimulant drugs is partly substance-dependent and partly related to specific routes of administration. Problematic consumption patterns and dependence, for example, happen more commonly among people who inject or smoke stimulants – regardless of the substance they use (EMCDDA 2018a)." (Rigoni et al., 2018, p. 18) • "Grund et al. (2010) have created an overview of the relation between (injection) stimulant use and HIV and HCV (Grund et al. 2010, 194–95). More recently, the UNODC (2017) also published a systematic literature review on the relation between stimulant use and HIV." (Rigoni et al., 2018, p. 18) • Compared to people who inject heroin "An additional risk for people who inject stimulants is that they often inject more frequently, are more likely to share needles and syringes, often have more chaotic injecting practices and also engage more frequently in risky sexual activities (Grund et al. 2010; Folch et al. 2009)." (Rigoni et al., 2018, p. 18) • "Damage to the lungs is strongly linked to smoking stimulants, most notably smoked cocaine (Jean-Paul Grund et al. 2010). People who smoke stimulants can also transmit diseases by sharing pipes and other materials. For instance, metal and glass pipe" (Rigoni et al., 2018, p. 18)

	• "The prevalence of methamphetamine smoking and injecting was comparable during the examined decade of treatment admissions in at least one study [3]." (Imtiaz et al., 2020, p. 1) • Sex related HIV risk behaviors: differential risks among injection drug users, crack smokers, and injection drug users who smoke crack (Booth et al., 2000)
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

No systematic reviews or meta-analyses were found on the benefits and harms of screening stimulant users for route of administration.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Kiluk 2015[1]	Pooled analysis of 5 RCTs 1-, 3-, 6-, 12-month follow-up Various settings	Various behavioral and pharmacologic treatments for cocaine dependence	N=434 adults with cocaine use disorder (DSM-IV) recruited from 5 RCTs in different populations (eg, general outpatient, methadone maintenance, comorbid alcohol and cocaine dependent). Subgroup comparison: Cocaine smokers (80%) vs. intranasal users	"Overall, results indicated better cocaine use outcomes both during the treatment phase and through a 12-month follow-up period for intranasal users compared to smokers, although not all differences reached statistical significance." **Treatment retention**: Intranasal users remained in treatment longer ($p < 0.05$). **Cocaine use**: Trend with intranasal users reporting a greater decrease in the frequency of cocaine use over time compared to smokers (p=006). **Cocaine use severity** (ASI): Intranasal users' ASI cocaine	

				composite score decreased more than smokers ($p<0.05$). **Dependence severity** (ASI): NSD in other composite scores except Employment.	
Sterk 2003[2]	RCT 6-month follow-up USA Community	(1) **Enhanced Motivation:** 4-session gender-specific motivational HIV psychoeducation intervention. Emphasized motivation for positive behavioral change and removing barriers that prevent change. (2) **Enhanced Negotiation**: 4-session gender-specific Negotiation HIV psychoeducation intervention. Emphasized negotiation skills, assertiveness, as well as conflict resolution. (3) **Control:** NIDA Standard HIV Intervention	N=333 out-of-treatment HIV negative, heterosexually active African-American adult women who smoked crack cocaine or injected drugs at least three times in the prior 30 days recruited from urban communities using street outreach techniques. Subgroup comparison: IDUs who did not smoke crack (n=26; 27% injected crack in prior 30 days), IDUs who did smoke crack (n=44), and crack smokers who did not inject (n= 263).	Follow-up rate 96% Overall, women in the Smoking & IDU category were less responsive to the intervention than those the other drug using groups, and women in the Smoking only group were less responsive than those the IDU only group. **Crack use frequency**: Greater reduction in Smoking only vs Smoking & IDU group ($p<0.001$). Greater reduction in IDU only vs Smoking & IDU group ($p<0.01$). **Injection drug use**: Greater frequency reduction in IDU only vs Smoking & IDU group ($p<0.01$). **Sharing needles**: NSD **Sex while high**: Greater reduction in Smoking only vs Smoking & IDU group ($p<0.05$). Greater reduction in IDU only vs Smoking & IDU group ($p<0.001$).	Response to an HIV risk reduction intervention varied according to drug uses and route of drug administration. Study participants from: Sterk 2003a; Sterk 2003b
Toth 2016[3]	cross-section Denmark Supervised consumption facility (SCF)	Self-reported referral to medical help by SCF staff	n=154 PWUD who used at least one of five SCFs; 10% < 30 years; 25% female	**Receipt of treatment for condition** (Self-reported yes vs. no): Those advised to seek medical help by staff for a medical condition were more likely to receive treatment for the condition than who were not advised to seek treatment	In systematic review Kennedy 2017[4]

				for a condition (51.3 vs. 25.7%, p = 0.003).	

ASI = Addiction Severity Index brief version (McLellan et al., 1992)

Evidence-Based Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Non-Systematic Reviews & Commentary

Source	Recommendation	Comments
Chan 2022[5]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE – Route of administration • For people who use stimulants, clinicians should ask the route of delivery to further tailor HR counseling. • The addiction potential of methamphetamine increases in relation to how it is used in the following order: oral use, snorting, smoking, injection (i.v.). • Oral intake of methamphetamine is thought to be the lowest-risk route of administration.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Increased risk of infection by route and substance	Complications of use will vary by route Overall health considerations by drug (eg, cocaine and levamisole)	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	No plausible undesirable effects	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	May depend on clinician education about regional variations and trends in drug use and complications that may result (eg, zylocene adulteration in opiates)	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
*Equity: What would be the impact on health inequities?		

Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Clinicians may be unfamiliar with asking these questions	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Requires clinician education, but similar to other diseases and conditions.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Health complications of stimulant use will vary depending on route of administration

Subgroup Considerations

No other subgroup considerations noted

Implementation Considerations

Requires clinician education, but similar to other diseases and conditions for which specific types of questions are necessary and useful

References

1. Kiluk BD, Serafini K, Malin-Mayor B, Babuscio TA, Nich C, Carroll KM. Prompted to treatment by the criminal justice system: Relationships with treatment retention and outcome among cocaine users. *Am J Addict*. 2015;24(3):225-232. Doi:10.1111/ajad.12208
2. Sterk CE, Theall KP, Elifson KW. Who's getting the message? Intervention response rates among women who inject drugs and/or smoke crack cocaine. *Prev Med*. 2003;37(2):119-128. Doi:10.1016/S0091-7435(03)00090-2
3. Toth EC, Tegner J, Lauridsen S, Kappel N. A cross-sectional national survey assessing self-reported drug intake behavior, contact with the primary sector and drug treatment among service users of Danish drug consumption rooms. *Harm Reduct J*. 2016;13(1):27. Doi:10.1186/s12954-016-0115-0
4. Kennedy MC, Karamouzian M, Kerr T. Public Health and Public Order Outcomes Associated with Supervised Drug Consumption Facilities: a Systematic Review. *Curr HIV/AIDS Rep*. 2017;14(5):161-183. Doi:10.1007/s11904-017-0363-y
5. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. https://doi.org/10.1016/j.mcna.2021.09.002

Table 51. Assess Risky Patterns - Prevention

Recommendation: For patients who screen positive for stimulant misuse: Clinicians should assess the following to determine harm reduction service and counseling needs:

a. Risky patterns of stimulant use, including:
   i. frequency and amount of use including binge use;
   ii. use of stimulants with no one else present;
   iii. concurrent use of prescribed and nonprescribed medications and other substances, particularly opioids, alcohol, and other central nervous system depressants;
   iv. history of overdose;
   v. history of stimulant-related emergency department visits and hospitalizations.

Clinical Question Summary Table

Clinical Question	What are effective strategies for assessing risky patterns of stimulant use?
Population	Patients who screen positive for stimulant misuse
Intervention	Strategies for assessing route of administration and related history of complications
Comparison	TAU (not addressed)
Main Outcomes	Health outcomes
Setting	Outpatient settings
Background & Definitions	Evidence suggests that certain patterns of use lead to more negative consequences
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

No research was identified.

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Potentially large depending on findings. Identifying highly risky patterns could lead to large benefits following harm reduction intervention. Benefits will vary by patient acceptance of intervention. Large: use alone	☐ None ☐ Small ☐ Moderate ☒ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	No plausible undesirable effects.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence that some patterns of use lead to more negative consequences. No evidence found on effectiveness of clinical interview to identify risky patterns.	High given the evidence on negative consequences, but will depend on effective patient history, interview, and review of medical records	☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Highly preferred	☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
Recent trends suggest increasing adverse outcomes related to race and other social inequities that lead to health care disparity. Intervening with individuals at greatest risk can lead to reductions in health inequity.	Assuming that assessed needs are addressed by clinical intervention.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Assuming that assessed needs are addressed by clinical intervention.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Information obtained will come from patient history, interview, and review of medical records, but similar to other diseases and conditions.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Potentially large depending on findings. Identifying highly risky patterns could lead to large benefits following harm reduction intervention. Benefits will vary by patient acceptance of intervention.

Subgroup Considerations

Recent trends suggest increasing adverse outcomes related to race and other social inequities that lead to health care disparity. Intervening with individuals at greatest risk can lead to reductions in health inequity.

Implementation Considerations

Requires clinician education, but similar to other diseases and conditions for which specific types of questions are necessary and useful

Table 52. Assess Risky Sex – Prevention

Recommendation: For patients who screen positive for stimulant misuse:

a. Clinicians should assess the following to determine harm reduction service and counseling needs:
   i. risky sexual behaviors.

Clinical Question Summary

Clinical Question	What are effective strategies for assessing risky sexual behaviors in patients with SUD/StUD?
Population	Patients who screen positive for stimulant misuse
Intervention	Assess risky sexual behaviors
Comparison	TAU (no assessment)
Main Outcomes	Improved sexual health outcomes
Setting	Outpatient settings
Background & Definitions	As evidence suggests that risky sexual behaviors are more prevalent in individuals who use stimulants, clinicians should gather information from the patient about their sexual behaviors to properly determine psychosocial and harm reduction service needs
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
			Screening for PrEP Identifying risky behaviors	
Important Outcomes				

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Dunn 2016[1]	Psychometric development USA Phase 1: SUD treatment settings Phase 2: Online survey	**BRAID** (Behavioral Risk Assessment for Infectious Diseases): 5 factor, 14 item self-report instrument to assess infectious disease risk behaviors (injection and non-injection) among alcohol and other drug users	N=998 adults with alcohol/substance use. Primary substance cocaine/crack (42%), ATS/MA (12%). Participants reporting ever injecting a drug 26%.	Phase 1: Factor analysis revealed a 12-item solution with 5 factors (**Unprotected Sex with Risky Partners, Injection Use, Sex on Cocaine/Crack, Condom Availability, and Intranasal Drug Use**). Infectious disease history was positively associated with Injection Use (Sample 1) and Unprotected Sex with Risky Partners (Sample 2) and negatively associated with Intranasal Drug Use (Samples 1 and 2). Phase 2: Added additional injection-related items and confirmed the factor structure of the existing BRAID.	
Hatch-Maillette 2019[2]	2x2 factorial repeated measures 3-month follow-up USA	(1) **Basic training**: 2-hour sexual risk conversation training (2) **Enhanced training**: 10 hours plus ongoing coaching.	N=60 counselors providing individual therapy at two opioid treatment programs (OTP) and two psychosocial outpatient programs	"Counselors receiving Enhanced training (n =28) showed significant improvements compared to their Basic training counterparts (n = 32) in self-efficacy, use of reflections, and use of decision-making and communication strategies with standardized patients. These improvements were maintained from post-training to 3-month follow-up."	
Smith 2012[3]		**ARCH-MSM** (Assessing the Risk of Contracting HIV in			

		MSM) previously called HIRI-MSM			

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):192. doi:10.15585/mmwr.rr7004a1

Centers for Disease Control and Prevention. *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2021 Update: A Clinical Practice Guideline*. Centers for Disease Control and Prevention (CDC); 2021:108.

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Additional Resources from Guidelines

Source	Resource	Comments
Centers for Disease Control and Prevention 2021[4]	**Sexually Transmitted Infections Treatment Guidelines, 2021 (Workowski et al., 2021)** • Guidance for obtaining a sexual history is available at the Division of STD Prevention resource page (https://www.cdc.gov/std/treatment/resources. htm) and in the curriculum provided by the National Network of STD Clinical Prevention Training Centers (https://www. nnptc.org) • tool for STI risk assessment suitable for primary care settings (https://www.cdc.gov/std/products/provider-pocket-guides. htm) • Additional information about gaining cultural competency when working with certain populations (eg, gay, bisexual, or other men who have sex with men [MSM]; women who have sex with women [WSW] or with women and men [WSWM]; or transgender men and women or adolescents) is available in sections of these guidelines related to these populations • For a more complete sexual history that includes information about a patient's gender identity, partners, sexual practices, HIV/STI protective practices, past history of STDs, and pregnancy intentions/preventive methods (https://www.cdc.gov/std/treatment/sexualhistory.pdf)	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Risky sexual behaviors are more prevalent in stimulant users. How effective is screening at identifying risky sexual behavior?	Identifying individuals through screening to provide prevention services (PrEP, education). Size of desirable effects will depend on severity and extent of underlying risk. Screening for risky sexual behaviors interacts with factors such as IPV/trauma, race, sex, and gender identification. Subgroup population differences may influence the intervention given (eg, Transgender, IPV/trauma history, HIV+ patient/partner).	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
No specific evidence found in the literature review. There is research linking stigma and bias in addiction to quality of health care services and access to care.	Possibility of patients experiencing feelings of stigma or bias. May depend on clinician expertise in asking questions. Possibility of privacy/confidentiality violations with ERH, charting. However, likelihood of this happening is plausibly low.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
See above.	While there is a potential for undesirable effects to occur, the benefits outweigh the risks. Also, some vulnerable groups with higher underlying prevalence may benefit from screening even more than the general population through detection and intervention.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence Summary	*Additional Considerations*	*Judgment*
Indirect, based on the evidence from interventions that could be implemented based on screening rather than screening itself.	Extrapolation from indirect evidence. Refer	☐ No evidence ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Plausible that patients value the outcomes, particularly if they utilize the interventions.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Structural and institutional biases may increase the likelihood of undesirable outcomes occurring for already vulnerable populations.	☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	No plausible reasons	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	It may take additional time.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

While there is a potential for undesirable effects to occur, the benefits outweigh the risks. Also, some vulnerable groups with higher underlying prevalence may benefit from screening even more than the general population through detection and intervention.

Subgroup Considerations

None noted

Implementation Considerations

Additional screening may take extra time

References

1. Dunn KE, Barrett FS, Herrmann ES, Plebani JG, Sigmon SC, Johnson MW. Behavioral risk assessment for infectious diseases (BRAID): Self-report instrument to assess injection and noninjection risk behaviors in substance users. *Drug Alcohol Depend*. 2016;168:69-75. doi:10.1016/j.drugalcdep.2016.07.032
2. Hatch-Maillette MA, Harwick R, Baer JS, et al. Increasing substance use disorder counselors' self-efficacy and skills in talking to patients about sex and HIV risk: A randomized training trial. *Drug Alcohol Depend*. 2019;199:76-84. doi:10.1016/j.drugalcdep.2019.02.023
3. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States. *J Acquir Immune Defic Syndr*. 2012;60(4):421-427. doi:10.1097/QAI.0b013e318256b2f6
4. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):192. doi:10.15585/mmwr.rr7004a1

Early Intervention for Risky Stimulant Use

Table 53. Early Intervention SBI

Recommendation: Clinicians should consider providing a brief intervention to patients with any risky stimulant use using motivational interviewing techniques to encourage patients to reduce or stop their use.

Clinical Question Summary Table

Clinical Question	1. Do brief counseling interventions to reduce stimulant use, with or without referral, reduce stimulant use or improve other risky behaviors in patients with a positive screen? 2. What are the harms of brief interventions to reduce stimulant use in patients with a positive screen?
Population	Adult and adolescent patients with risky stimulant use
Intervention	Screening and brief intervention for risky stimulant use
Comparison	No screening and brief intervention
Main Outcomes	Stimulant use, Stimulant use risk behavior (eg, overdose risk, IDU risk), negative consequences of stimulant use, readiness to change
Setting	General clinical (medical, psychiatric) settings
Background & Definitions	Notes: • A nationally representative survey of Australian adults estimated that 50.4% of stimulant users would develop a stimulant use disorder within 14 years of onset of use (Marel et al., 2019). Pre-existing mental disorders were significantly associated with increased risk. •
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized control trial, **RR**: Risk ratio, **SMD**: Standardized mean difference, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Overdose risk behavior	N/A	Review of reviews: Farrell 2019[1] (Supplemental)	**Screening and Brief Intervention** • **Decreased** overdose risk behaviors IRR: 0.72 (0.59 – 0.87) o Bohnert 2016 (OUD, Brief motivational interviewing) • Review rating of evidence: **Level of evidence: B*** (evidence from one or two RCTs only. *Evidence drawn from people who inject drugs and not specific to stimulant users, however we have no reason to believe this intervention would operate differently among stimulant users specifically.	Review focused on **stimulant related** harms. Opioid users

Stimulant use	N/A	Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use** vs Other Intervention (attentional control/wait-list/TAU) in **primary care**
			Included study designs: RCTs, case-crossover trials
			Identified studies all of non-screen detected populations (ie, tx/help-seeking)
			• **No effect** on stimulant abstinence rate at 6-12 months in 4 trials (RR=1.45 [0.86, 2.56]) with significant heterogeneity (I^2=65%, p=0.03).
			  o Baker 2001 (RCT, n=64 community-recruited Australian adult regular ATS use, 4-session in-person MI/CBT vs Control)
			  o Baker 2005 (RCT, n=215 community-recruited Australian adult regular ATS use, 2-session in-person MI/CBT vs Control)
			  o Marsden 2006 (RCT, n=342 community-recruited UK Adol/YAdult regular stimulant use, 1-session in-person MI vs Control)
			  o Tait 2015 (n=160 community-recruited Australian YAdul ATS use, 3-session computer-delivered MET/CBT vs Wait-list)
			• **No effect** on cocaine use days at 6-12 months in 1 trial (MD= −0.47 [−1.17, 0.24])
			  o Stein 2009 (RCT, n=198 community-recruited US adult regular cocaine use, 4-session in-person MI vs Control)
			• **No effect** on amphetamine use severity in 1 trial, (SMD=0.10 [−0.35, 0.54])
			  o Tait 2015 (n=160 community-recruited Australian YAdult ATS use, 3-session computer-delivered MET/CBT vs Wait-list)
				USPSTF systematic review of screening in primary care.
				
				Adol=Adolescents (age 12-17)
				YAdults=Young Adults

		Review of reviews: Farrell 2019[1] (Supplemental)	**Screening and Brief Intervention** • **No effect** on reducing stimulant use based on 1 RCT o Saitz 2014 (RCT, n=528 adults risky drug use [19% cocaine] Primary Care, Screening + MI vs Screening + BNI vs Screening alone)	

			• Review rating of evidence: **Level of evidence: B** (evidence from one or two randomized controlled trials only)	
		Meta-analysis: Sayegh 2017[3] (Moderate)	**Motivational Interviewing** • **No effect** on UDS-confirmed stimulant use 0-3 months following the intervention across 3 studies (p=0.37). o Ingersoll 2011 (Crack use tx-seeking HIV+) d= -0.27 [-0.88, 0.35] o McKee 2007 (Cocaine use tx seeking) d= -0.24 [-0.75, 0.28] o Rohsenow 2004 (Cocaine use tx seeking) d=0.05 [-0.49, 0.59]	
Important Outcomes				
Drug use	N/A	Meta-analysis: Tanner-Smith 2022[4] (Supplemental)	**Drug-targeted brief interventions** vs less active comparison condition (no treatment, sham, TAU) in **general medical settings** • **Decreased** multiple drug/mixed substance use (16 RCTs, SMD=0.08 [0.002, 0.15]; I^2= 27.28%). • Individual studies not listed.	
		Meta-analysis: Tran 2021[5] (Supplemental)	**Positive for CBT** compared to Control (No Intervention) in number of days using drugs in prior 30 days. Reduced by 3.7 more days compared to control groups with no intervention (2 studies, n = 337, 95% CI −5.59 to −1.81, p<0.001; I-squared=0%, p=0.72). • Marinelli-Casey 2008 (n=287 MaUD, Drug court vs non-Drug court) RoB high • Martin 2010 (n=50 MDMA use, 1-session Brief CBT vs Wait-list) RoB low **Author assessment of evidence quality** Confidence in trial end estimate: High; Risk of bias: not serious; Inconsistency: not serious; Indirectness: not serious; Imprecision: not serious; Other considerations: none	ATStUD
		Meta-analysis: Tran 2021[5] (Supplemental)	**Positive for CBT** compared to Control (No Intervention) in % drug use at the end of treatment RR 0.76, 95% CI 0.64 to 0.91, p=0.002; I-squared=22%, p=0.27; 6 studies, n=725 • **Baker 2001 RoB high** • **Baker 2005 (Brief CBT) RoB low** • **Lea 2017 RoB high** • **Santos 2014** (n=326 substance-using MSM, Brief HIV risk behavior counseling + Control vs Control=rapid HIV testing) **RoB high** • **Shoptaw 2008** (n=127 AUD/StUD MSM, 16 wk G-CBT vs GSST) **RoB high** • **Smout 2010** (n=104 MaUD/use, 3 mo CBT vs ACT) **RoB high** **Author assessment of evidence quality** Confidence in trial end estimate: High; Risk of bias: not serious; Inconsistency: not serious; Indirectness: not serious; Imprecision: not serious; Other considerations: strong association all plausible residual confounding would reduce the demonstrated effect	ATStUD

		Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use** vs Other Intervention (control/wait-list/TAU) **in primary care** Including results for screen-detected and non-screen detected populations o **Higher** drug abstinence rate at 3- to 4-month follow-up (15 trials, n=3636, 419/2134 vs 218/1502, RR 1.60, 95% CI 1.24-2.13; ARD=9%, 95% CI 5%-15%]; I^2=57%, p=0.001) o No effect in screen-detected populations (8 trials, 203/1089 vs 148/823, RR 1.28, 95% CI 0.97-1.84, p=0.08; I^2=57%, p=0.022). o Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) o Gelberg 2017 (n=65 moderate-risk [ASSIST 4-26] drug using) [9% cocaine, 8% ATS] adults in primary care, 1-session in-person BI + 2 booster calls vs Attention Control) o Ondersma 2007 (n=107 any illicit drug use in US women in hospital postdelivery recovery, 1-session computer MI + 2 booster mailings vs Assessment only) o Ondersma 2014 (n=143 any drug use in US women in hospital postdelivery recovery, 1-session computer MET vs Attention Control) o Ondersma 2018 (n=500 any [WIDUS ≥3] drug use in US women in hospital postdelivery recovery, 1-session computer BI on parenting vs Attention Control) o Tzilos Wernette 2018 (n=59 any [T-ACE or SURP-P] alcohol/drug use in pregnant women in OB/Gyn, 1-session computer MI + 1 booster vs Attention Control) o Yonkers 2012 (n=183 any [TWEAK ≥3] drug use in US pregnant women in Ob/Gyn, 6-session computer MET/CBT vs Brief Advice) o Zahradnik 2009 (n=126 Rx drug misuse/dependent German adults in hospital, 1 in-person MI + phone booster vs Control) o Positive effect in non-screen detected populations (treatment seeking) (7 trials, 216/1045 vs 70/679, RR=2.1, 05% CI 1.52-2.90, p<0.001; I-squared=28%, p=0.22) o Babor 2004 (n=450 cannabis dependent US adults, 9-session MET/CBT vs 2-session MET vs Waitlist) o Gates 2012 (n=149 cannabis using Australian adolescent/young adults, 4-session phone MI/CBT vs Waitlist) o McCambridge 2004 (n=200 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) o McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control)	USPSTF systematic review of screening in primary care. ARD = absolute risk difference ED=Emergency department Preg = Pregnant SMD = Standardized mean difference

			○ Rooke 2013 (n=230 cannabis using Australian adults, 6-module web-based MI/CBT vs Control) ○ Schaub 2015 (n=308 cannabis using US adults, 8-module web-based MI/CBT w/ chat vs w/out chat vs Waitlist) ○ Stephens 2000 (n=291 cannabis using US adults, 14-session in-person CBT vs 2-session in-person MI vs Waitlist) ○ **Higher** drug abstinence rate at **6- to 12-month** follow-up (14 RCTs, n=4031, 535/2420 vs 352/1871, RR 1.31, 95% CI 1.10 to 1.55, p=0.002; I^2=38%, p=0.07; ARD=6%, 95% CI 2%-10%) ○ No effect in screen-detected populations (7 trials, 298/1687 vs 204 vs 1256, RR 1.17, 95% CI 0.99 to 1.38, p=0.06, I^2=2%, p=0.41) ○ Bernstein 2005 (n=1175 moderate-to-severe [DAST-10 ≥3] cocaine/heroin using [93% cocaine] US adults in primary care, 1 in-person MI + phone booster vs Control) ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) ○ Ondersma 2014 (n=143 any drug use in US women in hospital postdelivery recovery, 1-session computer MET vs Attention Control) ○ Ondersma 2018 (n=500 any [WIDUS ≥3] drug use in US women in hospital postdelivery recovery, 1-session computer BI on parenting vs Attention Control) ○ Saitz 2014 (RCT, n=528 risky [ASSIST ≥4] drug using [19% cocaine] US adults in primary care, Screening + MI vs Screening + BNI vs Screening alone) ○ Zahradnik 2009 (n=126 Rx drug misuse/dependent German adults in hospital, 1 in-person MI + phone booster vs Control) ○ Positive effect in non-screen detected populations (treatment seeking) (7 trials, 237/733 vs 148/615, RR 1.51, 95% CI 1.14 to 2.37, p=0.008; I^2=57%, p=0.03) ○ Baker 2001 (n=64 community-recruited stimulant using Australian adults, 4-session in-person MI/CBT vs Control) ○ Baker 2005 (n=215 community-recruited stimulant using Australian adults, 2-session in-person MI/CBT vs Control) ○ Copeland 2001 (n=173 cannabis using Australian adults, 1-session in-person vs Wait-list) ○ Marsden 2006 (RCT, n=342 community-recruited regular stimulant using UK adolescent/young adults, 1-session in-person MI vs Control)	

			○ McCambridge 2004 (n=200 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ Tait 2015 (RCT, n=160 community-recruited ATS using Australian young adults, 3-session computer-delivered MET/CBT vs Wait-list) ○ **Decreased** drug use days in the past 7 days at **3- to 4-month** follow-up (19 trials, n=5085, MD –0.49, 95% CI –0.85 to –0.13; I^2=89%, p<0.001). ○ In screen-detected populations (9 trials, n=3421, MD −0.10 [−0.31, 0.12]; I^2=45.8%, p=0.044). ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Blow 2017 (n=780 risky [ASSIST ≥4] drug using US adults in ED, 1-session in-person MI vs 1-session computer MI vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) ○ Lee 2010 (n=341 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Lee 2013 (n=212 cannabis using US college age students, 1-session in-person personalized feedback vs Control) ○ Martino 2018 (n=439 moderate risk [ASSIST 4-26] drug using women primary care reproductive health visit, 1-session in-person BI vs 1-session computer BI vs Control) ○ Palfai 2014 (n=123 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Roy-Byrne 2014 (n=868 drug [42% stimulants] using adults in primary care, 1-session MI + booster call vs Control) ○ Woolard 2013 (n=515 alcohol & cannabis using US adults, 2-session in-person MI vs Control) ○ In non-screen detected populations (treatment seeking) (10 trials, MD −0.91, 95% CI −1.52 to −0.31; I^2=86%, p<0.001). ○ Babor 2004 (n=450 cannabis dependent US adults, 9-session MET/CBT vs 2-session MET vs Waitlist) ○ de Dios 2012 (n=34 cannabis using US young adults, 2-session in-person BI vs Control) ○ de Gee 2014 (n=119 cannabis using US adolescents/young adults, 2-session in-person MI vs Control) ○ Fischer 2012 & 2013 (n=134 cannabis using adults, 1-session in-person BI vs Control)	

			○ Gates 2012 (n=149 cannabis using Australian adolescent/young adults, 4-session phone MI/CBT vs Waitlist) ○ Martin 2008 (n=40 cannabis using Australian adolescents, 2-session in-person MI vs Control)) ○ McCambridge 2008 (n=326 cannabis using UK adolescent/young adults, 1-session in-person MI vs Control) ○ Rooke 2013 (n=230 cannabis using Australian adults, 6-module web-based MI/CBT vs Control) ○ Schaub 2015 (n=308 cannabis using US adults, 8-module web-based MI/CBT w/ chat vs w/out chat vs Waitlist) ○ Stephens 2000 (n=291 cannabis using US adults, 14-session in-person CBT vs 2-session in-person MI vs Waitlist) ○ **No effect** on drug use in prior 7 days at **6- to 12-month** follow-up (10 trials, MD 0.00, 95% CI −0.24 to 0.22; I^2=42%, p=0.019) ○ Bernstein 2009 (n=139 cannabis using US adolescent/young adults in ED, 1 in-person MI + phone booster vs Control) ○ Blow 2017 (n=780 risky [ASSIST ≥4] drug using US adults in ED, 1-session in-person MI vs 1-session computer MI vs Control) ○ Bogenschutz 2014 (n=854 moderate-to-severe [DAST-10 ≥3] drug using [27% cocaine, 4% MA] US adults in ED, 1 in-person MI + 2 phone booster vs Minimal Control) ○ Lee 2010 (n=341 cannabis using US college age students, 1-session computer-delivered personalized feedback vs Control) ○ Lee 2013 (n=212 cannabis using US college age students, 1-session in-person personalized feedback vs Control) ○ Martino 2018 (n=439 moderate risk [ASSIST 4-26] drug using women primary care reproductive health visit, 1-session in-person BI vs 1-session computer BI vs Control) ○ Paffai 2014 (n=123 cannabis using US college students, 1-session computer-delivered personalized feedback vs Control) ○ Roy-Byrne 2014 (n=868 drug [42% stimulants] using adults in primary care, 1-session MI + booster call vs Control) ○ Saitz 2014 (RCT, n=528 risky [ASSIST ≥4] drug using [19% cocaine] US adults in primary care, Screening + MI vs Screening + BNI vs Screening alone) ○ Woolard 2013 (n=515 alcohol & cannabis using US adults, 2-session in-person MI vs Control)	
			Brief interventions (1-2 sessions each < 1 hr) for unhealthy drug use vs Other (usually an attentional control, wait-list, or TAU) in **primary care** Includes results for screen-detected and non-screen detected populations	

			• **Higher** drug abstinence rate at 3- to 4-months (10 trials, 244/1413 vs 161/1140, RR 1.47, 95% CI 1.11 to 1.94, p=0.007; I^2=61%, p=0.02) o McCambridge 2004; McCambridge 2008; Babor 2004 arm; Bogenschulz 2014; Gelberg 2017, Tzilos Wernette 2018; Ondersma 2007; Ondersma 2014; Ondersma 2018; Zahradnik 2009 • **Higher** drug abstinence rate at 6-12 months (11 trials, 469/2175 vs 336/1746, RR 1.22, 95% CI 1.08 to 1.39, p=0.002; I^2=5%, p=0.39) o Baker 2005; Marsden 2006; McCambridge 2004; McCambridge 2008; Bernstein 2005; Bernstein 2009; Bogenschulz 2014; Ondersma 2014; Ondersma 2018; Saitz 2014; Zahradnik 2009 • Drug use days at 3-4 months in (9 trials, MD= −0.13 [−0.36, 0.12]; I^2=42%) • Drug use days at 6-12 months (11 trials, MD= −0.06 [−0.24, 0.11]; I^2=0%)	
Drug use consequences	N/A	Meta-analysis: Tanner-Smith 2022[4] (Supplemental)	**Drug-targeted brief interventions vs less active comparison condition (eg no treatment, sham, and treatment as usual) in general medical settings** • **No effect** on drug use consequences between across 12 RCTs. o Individual studies not listed.	
Drug use severity	N/A	Meta-analysis: Patnode 2020[2] [JAMA] (Supplemental)	**Psychosocial Intervention for unhealthy drug use vs Other Intervention (control/wait-list/TAU) in primary care** • **Lower** drug use severity **at 3-4 months** (17 trials, n=4437, SMD -0.18, 95% CI -0.32 to -0.05; I-squared=73%, p<0.001) o Screen-detected populations: **No effect** on drug use severity **at 3-4 months** (9 trials, SMD -0.05, 95% CI -0.15 to 0.05; I^2=17%, p=0.295) • **No effect** on drug use severity at **6-12 months** (13 trials, n=3798, SMD -0.1, 95% CI -0.15 to 0.06; I-squared=65%, p=0.001) o Screen-detected populations: **No effect** on drug use severity at **6-12 months** (9 trials, SMD -0.03, 95% CI -0.15 to 0.02; I^2=40%, p=0.099)	USPSTF systematic review of screening in primary care.
			Brief interventions (1-2 sessions each < 1 hr) vs Other (attentional control, wait-list, or TAU) in primary care • **No effect** on drug use severity at 6-12 months (10 trials, SMD −0.02, 95% CI −0.13 to 0.06	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Bernstein 2005[6] (Supplemental)	RCT 6-mo follow-up USA Primary care	**(1) MI**: One motivational interview session (10-45 min) with a peer interventionist including active referral & referral handout followed in 10 days by one 5-10 min telephone booster call **(2) Control**: Referral handout	N=1175 adults reporting last 30-day cocaine/heroin use (93% cocaine) and DAST10 score ≥ 3 (moderate-to severe problems related to drug use).	**Follow-up**: NSD between groups in follow-up rate (83% vs 81%) **Cocaine abstinence**: Of those cocaine-positive at baseline (n=720), higher abstinence in MI group at follow-up compared to controls (22.3% vs 16.9%, adjusted OR=1.51 [1.01, 2.24, p=0.45). **Cocaine use** (hair sample [ng/10 mg]): Trend for greater reduction in hair levels in MI compared to control group (MD= -29% vs -4%, p=0.058). **Addiction severity** (ASI subscale): Among participants with pre- and post-scores, trend for greater score reduction in MI group (n=962, 49% vs 46%, p=0.06). **Treatment system contact**: NSD among participants abstinent at 6 months (39% vs 37%).	Patnode (2020a)[2] [JAMA] Quality rating: Good Also see EtDT Prev Refer to Tx, EtDT Prev MI-BI
Bogenschutz 2014[7] (Supplemental)	RCT 12-mo follow-up USA Emergency Department	(1) **SBIRT**: Screening, assessment, brief intervention, and referral to treatment if indicated with up to 2 telephone boosters (2) **SRT**: Screening, assessment, and referral to treatment if indicated (3) **SO**: Minimal screening only and informational pamphlet	N=1285 adults (30% female, 50% white) with DAST10 score ≥ 3 (moderate-to severe problems related to drug use). Primary substance 27% cocaine, 4% MA, 3% prescription stimulants.	Follow-up rate 81% at 12 months **Cocaine use** (self-report): Among those reporting primary cocaine use (n=349), NSD in number of days using cocaine in past 30 days at the 3-, 6- or 12-month follow-up. **Primary drug use** (hair): Among participants with samples (n= 858), more samples positive for primary drug in the SRT group (95%) compared to SBIRT (89%) or SO group (88%, p=0.02) at 3 months. NSD at other times. **Primary drug use** (self-report): NSD in number of days using primary drug in past 30 days at the 3-, 6- or 12-month follow-up. **Any drug use** (self-report): NSD in number of days using any drug in past 30 days at the 3-, 6- or 12-month follow-up.	
Gelberg 2015[8] (Supplemental)	RCT USA Primary care	(1) **SBI**: Screening, brief intervention (median 3-4 mins) with PCP, video, booklet, and up to 2 telephone boosters (20-30 mins each at 2- and 6-wks)	N=334 adult (63% male, 38% white) patients with ASSIST score 4-26 (moderately risky drug use indicating physician advice) recruited in FQHC primary care waiting rooms.	Follow-up rate 78% **Riskiest drug use*** (self-report): SBI patients reported using an average of 2.21 fewer days in the previous month than controls (MD= -2.21 [-3.76, -0.65], p=0.005).	*Initially recruited only stimulant users. Clinicians focused on stimulant use if it scored in the

		with health educators focused on highest scoring illicit drug (HSD)* (2) **Control**: Screening, cancer screening video and pamphlet	Excluded in SUD treatment starting more than 30 days ago or pregnant. 32% HSD was stimulants.	**Cocaine/crack use** (self-report): SBI patients reported using fewer days in the previous month than controls (n=67, MD=2.77 [-0.08, 5.63]) **MA/ATS use** (self-report): NSD (n=41, MD=0.01 [-7.57, 7.58])	risky range even if it was not the HSD.
Gerdtz 2020[9] (Supplemental)	Prospective observation Australia ER	Harm reduction advice and referral	N=457 (59% male) patients admitted to a behavioral assessment unit within an emergency department who tested positive or self-reported amphetamine-type stimulant use	**Referral acceptability:** Most patients accepted a referral to the alcohol and other drug clinician (85.6%, 95% CI 77.2–91.2).	Also see EtDT Prev Refer to Tx
Humeniuk 2012[10] (Supplemental)	RCT 3 mo Australia, Brazil, India, US Primary care	**(1) BI**: One 15 min brief intervention session based on ASSIST risk score **(2) Waitlist**	N=731 (USA=218) adolescents and adults (age 16-62) recruited at **primary care** with at least moderate-risk ASSIST score (4-26). Cocaine: 12.9% Amphetamines: 21.2% (44% female)	85% follow-up rate **Stimulant use** (ASSIST): Overall there was a significantly greater decrease in stimulant-specific substance involvement scores in BI compared to Waitlist groups (5.8 vs 3, F=9.4, p<0.005). However, there was NSD when the analysis was restricted to US participants (4.7 vs 5.3, F=0.08, p=0.8). There was a significant difference for Australian and Brazilian participants (India did not recruit stimulant users).	Patnode (2020) [AHRQ] guideline Quality rating: Fair ITT analysis
Karno 2021[11] (Cochrane RoB: Unclear)	RCT Study period: June 2013 to mid-2017 USA Outpatient (6 sites) & Inpatient (1 site)	**(1) SBIRT:** Single face-to-face session assessment with the ASSIST and BI tailored to ASSIST risk score. **(2) Control**: Health Education session (mean duration 20.3 minutes). **Not detected via universal screening of population.**	N= 718 adults (49.2% female, 47% non-white) seeking mental health treatment with an affective or psychotic disorder diagnosis and reported any use of stimulants, cannabis, or a heavy drinking day in the past 90 days. Excluded if received treatment for a SUD in the previous 90 days. 34.3% reported stimulant use in the prior 90 days. 52.4% of sample exceeded	**Stimulant abstinence** (self-report): No difference in odds of stimulant abstinence at the 3-, 6- or 12-month follow-up. **Stimulant use frequency** (self-report): Among participants who used stimulants during the follow-up period (n=299), SBIRT participants had fewer days of stimulant use compared to controls at 3-month follow-up (5.8 vs 9.8, OR = 0.58; 95% CI = 0.50 – 0.66). Effects remained at 6-month (4.7 vs 8.9) and 12-month follow-ups (6.1 vs 13.5). **Treatment access:** No difference in utilization of addiction treatment services for receipt of any service within 30 days of intervention (21.3% vs 24.3%) or total number of services received.	Statistical analysis for stimulant sub-group not determined a priori, so results are exploratory only. Also see EtDT Prev Refer to Tx

			threshold indicating severe mental illness (Kessler-6 score ≥ 13).		
Marsden 2006[12] (Supplemental)	RCT 6 mo follow-up UK Community	**(1) BI**: Self-assessment and single in-person motivational intervention session for 45-60 mins, manual guided, plus printed health risk information **(2) Control:** Self-assessment and printed health-risk information only	N=342 adolescents and young adults aged 16-22 yrs with **problematic** (at least four times over the past month) **MDMA or cocaine** use. Recruited via community advertising, outreach contact, and peer referral.	87.4% follow-up rate. No effect on cannabis or alcohol use. outcomes **Stimulant abstinence** (self-report + saliva testing): NSD. between groups in rate of prior 90-day abstinence from ecstasy, cocaine powder, or crack cocaine at 6-month follow up. **Stimulant use frequency**: NSD between groups in number of ecstasy and crack cocaine use days in previous 90 days at 6 months. Between group contrast for cocaine powder was significant (5.54 vs 7.40, p=0.01) but the effect size was not (d=0.15 [−0.06, 0.37]). **Stimulant use amount**: NSD between groups in amount of ecstasy, cocaine powder, or crack cocaine used in previous 90 days at 6 months.	In Li 2016[13] and Patnode (2020a)[2] [JAMA]Quality rating: Good Also see EtDT Adol BI-MI, EtDT Prev MI-BI, EtDT Prev Refer to Tx
McCambridge & Strang 2004[14] 2005[15] (Supplemental)	Cluster RCT 3, 12 mo follow-up UK Further education colleges	**(1) MI**: Single session (1 hour) in-person adapted from Miller & Rollnick 1991 and Rollnick 1992 **(2) TAU:** Usual education	N=200 adolescents and young adults aged 16-20 yrs with **weekly cannabis use or stimulant use** within the previous 3 months. Recruited by peer interviewers identified by school staff. Baseline stimulant use 23%. **At-risk population.**	89.5% followed up **Stimulant use**: NSD bw groups at 3-month follow-up (24% vs 41%) **Drug-associated problems**: Fewer MI participants reported experiencing problems attributed to the use of stimulants and other drugs (not cannabis, alcohol, tobacco) 3 months after intervention (12% vs 37%, p=0.009) **Readiness to change**: More MI participants reported increasing one motivational stage of change in relation to drug use higher than control group at 3 months after controlling for baseline stage (B = 0.76, p=0.004).	In Li 2016[13] and Patnode (2020a)[2] [JAMA]Quality rating: Fair Also see EtDT Adol BI-MI, EtDT Prev MI-BI, EtDT Prev Refer to Tx
Poblete 2017[16] (Supplemental)	RCT 3 month follow-up Chile Primary care, ED, police station	**(1) Brief intervention:** One 18 min in-person brief individual counseling session based on FRAMES. **(2) Control**: Pamphlet	N=806 adults (18-55) with ASSIST score 11 to 20 for alcohol or ASSIST score 4 to 20 for drug use (moderate risk). 19% received a cocaine-related brief intervention	Follow-up rate: 407/8-6 (62%) **Cocaine use severity** (ASSIST cocaine score, mean (SD): NSD between groups at 3 months (11.1 (9.2) vs 10.3 (8.5), MD=-0.11 (-3.69 to 3.48) **Drug use severity** (ASSIST total score, mean (SD): NSD between groups at 3 months (28.1 (14.4) vs 27.9 (15.0), MD=-0.13 (-1.47 to 1.74)	Patnode 2020 [AHRQ] guideline Also see EtDT Prev SBI & EtDT Prev Refer to Tx

Saitz 2014[17] (Supplemental)	RCT June 2009-Jan 2012 6-mo follow-up USA Primary Care	**(1) BNI:** Brief negotiated interview, a 10- to 15-minute structured interview conducted by health educators **(2) MI:** Adaptation of Motivational Interviewing, a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors **(3) No BI:** All participants received a list of SUDr treatment and mutual help resources.	N=528 adult with drug use ASSIST substance-specific scores ≥4 at an urban hospital-based primary care internal medicine practice. Baseline 19% reported cocaine as main drug.	**Cocaine use** (hair testing): NSD in % of participants with a positive hair test among participants with a sample (n=199). **Cocaine use amount** (hair testing): NSD in median quantitative level among participants with a sample (n=199). **Cocaine use frequency (self-report**: NSD in number of days of cocaine use in the past 30 days between BNI and Control (IRR=1.51 (0.78-2.91) p=0.31) and MI vs Control (IRR=1.41 (0.73-2.72) p=0.31) among participants with baseline cocaine use (n=97). **Cocaine use severity** (ASSIST): NSD **Drug use consequences**: NSD **Unsafe sex**: NSD **Injection drug use**: NSD **Mutual help meeting attendance**: NSD **Hospitalizations and ED visits**: NSD **Health care utilization for addiction or mental health reasons**: NSD	Also see EtDT Prev Refer to Tx
Smout 2010[18] (Supplemental)	Pre-post 3-month follow-up Australia Community	**Psychostimulant Check-Up:** Single-session brief intervention for stimulant users	N=80 adults (39% female) who used psychostimulants (**98% injected MA as usual route of administration**) in the previous month recruited though community advertisements and fliers. A majority of participants (55) were in the 'action' stage of readiness to change at baseline.	Follow-up rate 62% **MA use** (self-report): Fewer MA use days at follow up (15 vs 8.3, p<0.001). 25 reported no MA use in prior month at follow-up (28% of follow-up or 16% of baseline sample). 13% reported an increase in monthly consumption. 62% reported at least a 1g reduction in monthly MA use. **MA-related negative consequences** (self-report): Fewer experienced in the previous month at follow up (85 vs 59.5, p=0.002). **Injection use** (self-report): Fewer reported injection as the usual route of administration at follow up (n=11, 78% vs 55%, p=0.004). **Readiness to change**: No change in proportion of participants in each stage **Treatment engagement**: NSD in number of health service contacts in last month (2 vs 1.9, p=0.813) **Patient satisfaction**: 90% responding they were very satisfied or mostly satisfied with the Check-	Also see EtDT Prev IDU Counseling, EtDT Prev MI-BI, EtDT Prev Refer to Tx

				Up. 66% said it answered their questions, 92% increased awareness of services, and 91% would recommend it to friends.	

Existing Guidelines Table

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016.

Department of Veterans Affairs (VA), Department of Defense (DoD). VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Management of Substance Use Disorders Work Group. Department of Veteran Affairs & Department of Defense; 2016. https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Patnode CD, Perdue LA, Rushkin M, O'Connor EA. *Screening for Unhealthy Drug Use in Primary Care in Adolescents and Adults, Including Pregnant Persons: Updated Systematic Review for the U.S. Preventive Services Task Force*. Agency for Healthcare Research and Quality; 2020. Accessed April 29, 2022. http://www.ncbi.nlm.nih.gov/books/NBK558174/

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Unhealthy Drug Use: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(22):2301. doi:10.1001/jama.2020.8020

World Health Organization. Technical Brief 4 on Amphetamine-Type Stimulants (ATS): Therapeutic interventions for Users of Amphetamine-Type Stimulants (ATS).; 2011.

Other Resources Table

Source	Resource	Comments
	Finding Quality Treatment for Substance Use Disorders (https://store.samhsa.gov/product/ PEP18-TREATMENT-LOC): This resource is for people seeking behavioral health services and treatment for SUDs. It provides guidance on how to find a quality treatment center and the steps to complete before accessing treatment.	
	TIP 35: Enhancing Motivation for Change in Substance Use Disorder Treatment (https:// store.samhsa.gov/product/PEP19-02-01-003): TIP 35 describes the elements of motivational interventions, the five principles of MI, catalysts for changing behavior, and the stages of change that clients go through while working toward recovery from SUDs	
	Substance Abuse and Mental Health Services Administration. (2011). Screening, brief intervention and referral to treatment (SBIRT) in behavioral healthcare. Substance Abuse and Mental Health Services Administration.	
Smout 2008	Smout M, Krasnikow S, Longo M, Wickes W, Minniti R, Cahill S. Quickfix: Identity & Intervene in Psychostimulant Use in Primary Health Care (Updated 2015). Drug and Alcohol Services South Australia; 2008. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/quickfix+identity+intervene+in+psychostimulant+use+in+primary+health+care	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence that screening and brief intervention reduces stimulant use in adolescents and YAs based on a MA of 4 RCTs and 1 RCT (Saitz 2014)[16]. However, there is evidence that screening and brief intervention reduces use of a broader category of substances other than alcohol. Effect sizes ranged …	Brief intervention is a necessary first step to providing non-SBI harm reduction education and treatment for stimulant use, which can lead to other outcomes including reduction of harms stemming from use, increasing readiness to change, and increasing motivation for treatment.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Patients may be upset to be invited to discuss their substance use.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	The benefits of engaging the patient in meaningful harm reduction is significant and outweighs the risk of straining the therapeutic alliance.	☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Drawing from substance use reduction and other outcomes not covered in the literature review.	☐ Clinical judgment (no evidence) ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies

***Acceptability**: Is the option acceptable to key stakeholders?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Research Evidence Summary	*Additional Considerations*	*Judgment*
	Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

While no direct evidence exists to suggest that brief interventions are effective for stimulant use outcomes, it is a necessary first step to providing harm reduction education and treatment for stimulant use, which can reduce harms stemming from use and increase readiness to change and motivation for treatment.

Subgroup Considerations

None noted

Implementation Considerations

Screening creates a short-term time cost for clinicians. Highly variable by clinician and setting.

References

1. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
2. Patnode CD, Perdue LA, Rushkin M, et al. Screening for Unhealthy Drug Use: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;323(22):2310. doi:10.1001/jama.2019.21381
3. Sayegh CS, Huey SJ, Zara EJ, Jhaveri K. Follow-up treatment effects of contingency management and motivational interviewing on substance use: A meta-analysis. *Psychol Addict Behav*. 2017;31(4):403-414. doi:10/gbjxgb
4. Tanner-Smith EE, Parr NJ, Schweer-Collins M, Saitz R. Effects of brief substance use interventions delivered in general medical settings: a systematic review and meta-analysis. *Addict Abingdon Engl*. 2022;117(4):877-889. doi:10.1111/add.15674

5. Tran MTN, Luong QH, Le Minh G, Dunne MP, Baker P. Psychosocial Interventions for Amphetamine Type Stimulant Use Disorder: An Overview of Systematic Reviews. *Front Psychiatry*. 2021;12:512076. doi:10.3389/fpsyt.2021.512076
6. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend*. 2005;77(1):49-59. doi:10.1016/j.drugalcdep.2004.07.006
7. Bogenschutz MP, Donovan DM, Mandler RN, et al. Brief Intervention for Patients With Problematic Drug Use Presenting in Emergency Departments: A Randomized Clinical Trial. *JAMA Intern Med*. 2014;174(11):1736-1745. doi:10.1001/jamainternmed.2014.4052
8. Gelberg L, Andersen RM, Afifi AA, et al. Project QUIT (Quit Using Drugs Intervention Trial): A randomized controlled trial of a primary care-based multi-component brief intervention to reduce risky drug use. *Addict Abingdon Engl*. 2015;110(11):1777-1790. doi:10.1111/add.12993
9. Gerdtz M, Yap CYL, Daniel C, et al. Amphetamine-type stimulant use among patients admitted to the emergency department behavioural assessment unit: Screening and referral outcomes. *Int J Ment Health Nurs*. 2020;29(5):796-807. doi:10.1111/inm.12710
10. Humeniuk R, Ali R, Babor T, et al. A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries: Brief intervention for illicit drugs. *Addiction*. 2012;107(5):957-966. doi:10.1111/j.1360-0443.2011.03740.x
11. Karno MP, Rawson R, Rogers B, et al. Effect of screening, brief intervention and referral to treatment for unhealthy alcohol and other drug use in mental health treatment settings: a randomized controlled trial. *Addict Abingdon Engl*. 2021;116(1):159-169. doi:10/gn756x
12. Marsden J, Stillwell G, Barlow H, et al. An evaluation of a brief motivational intervention among young ecstasy and cocaine users: no effect on substance and alcohol use outcomes. *Addiction*. 2006;101(7):1014-1026. doi:10.1111/j.1360-0443.2006.01290.x
13. Li L, Zhu S, Tse N, Tse S, Wong P. Effectiveness of motivational interviewing to reduce illicit drug use in adolescents: a systematic review and meta-analysis. *Addiction*. 2016;111(5):795-805. doi:10.1111/add.13285
14. McCambridge J, Strang J. The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial. *Addiction*. 2004;99(1):39-52. doi:10.1111/j.1360-0443.2004.00564.x
15. McCambridge J, Strang J. Deterioration over time in effect of Motivational Interviewing in reducing drug consumption and related risk among young people. *Addiction*. 2005;100(4):470-478. doi:10.1111/j.1360-0443.2005.01013.x
16. Poblete F, Barticevic NA, Zuzulich MS, et al. A randomized controlled trial of a brief intervention for alcohol and drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in primary health care in Chile: ASSIST-BI for alcohol and drugs in Chile. *Addiction*. 2017;112(8):1462-1469. doi:10.1111/add.13808
17. Saitz R, Palfai TPA, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513. doi:10.1001/jama.2014.7862
18. Smout M, Longo M, Harrison S, et al. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. *Drug Alcohol Rev*. 2010;29(2):169-176. doi:10.1111/j.1465-3362.2009.00133.x

Table 54. Early Intervention Refer to Treatment

Recommendation:

1. For patients who screen positive for risky stimulant use, clinicians should conduct or offer a referral for comprehensive assessment and treatment for potential StUD with linkage support, including a warm handoff.
2. For patients who are ambivalent about referral for StUD assessment or treatment, clinicians should consider using interventions to enhance motivation for treatment (eg, MI, MET).

Clinical Question Summary Table

Clinical Question	a. Does referral to treatment reduce stimulant use or improve risky behaviors in patients with a positive screen? b. What are effective strategies for referral to treatment for StUD?
Population	Adult & adolescent patients
Intervention	Referral to assessment/treatment for stimulant use disorder (positive screen)
Comparison	TAU (No referral)
Main Outcomes	Accepted referral, initiated treatment, readiness to change
Setting	General clinical (medical, psychiatric) settings
Background & Definitions	Notes • Meta-analysis of the prevalence of barriers to accessing methamphetamine treatment in 6 studies (Cumming et al., 2016). The four most common psychosocial barriers were embarrassment or stigma (60%, 95% CI: 54–67%); belief that treatment was unnecessary (59%, 95% CI:54–65%); preferring to withdraw alone without assistance (55%, 95% CI:45–65); and privacy concerns (51%, 95% CI:44–59%). •
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NDS**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				

Health care utilization	N/A	Meta-analysis: Bray 2011[1] (Not assessed)	Alcohol screening and brief interventions targeting non-alcohol-dependent populations in primary care, ED, hospital. 29 studies (25 RCTs). No significant effect of alcohol **SBI** on outpatient health care utilization (follow-up range 6-120 months). Moderate heterogeneity (I-squared=53%, p=0.028). No significant effect of alcohol **SBI** on ED utilization (follow-up range 6-120 months). No significant heterogeneity (I-squared = 14%, p=0.326) No significant effect of alcohol **SBI** on inpatient health care utilization (follow-up range 6-120 months). Moderate to high heterogeneity (I-squared=69.7%, p=0.001). Inpatient care included any non-ED hospital stay or admission or inpatient treatment facility stay. AUD treatment not specified.	Alcohol use
		RCT: Saitz 2014[2]	NSD between **MI** and **Control** in hospitalizations and ED visits at 6 months (n=528 risky drug use in primary care)	Drug use
		Pre-post: Smout 2010[3]	NSD after **Psychostimulant Check-Up** in number of health service contacts in last month (n=80 psychostimulant use 2 vs 1.9, p=0.813)	Follow-up rate 62%
SUD treatment utilization	N/A	Meta-analysis: Glass 2015[4] (Not assessed)	No significant effect of **alcohol brief interventions** with adult and adolescents in general health-care settings on subsequent alcohol treatment initiation (9 RCTs, n=1930). No evidence of study heterogeneity. No significant effect for subgroup analyses which pooled results for adult, adolescent, high-severity, or low risk of bias studies.	Alcohol use
		RCT: Karno 2021[5]	NSD between **SBIRT** and **Control** in utilization of addiction treatment services for receipt of any service within 30 days of intervention (21.3% vs 24.3%) or total number of services received. (n=718 stimulant [34%], cannabis, or alcohol use)	
		RCT: Saitz 2014[2]	NSD between **MI** and **Control** in health care utilization for addiction or mental health reasons at 6 months (n=528 risky drug use in primary care)	Drug use
		RCT: Stein 2009[6]	NSD between **MI** and **Control** in any SUD treatment access at 6 months (n=198 cocaine use, 17.5% vs 19.8%, p=0.68). Not screen-detected, recruited via advertisement	
		RCT: Bernstein 2005[7]	NSD between **MI** and **Control** in treatment system contact among participants abstinent at 6 months (n=1175 cocaine [93%]/ heroin use in primary care).	
Help seeking	N/A	RCT: Tait 2015[8]	Actual help seeking increased for **MET/CBT**, declined for **Control** at 6 months (n=160 ATS use, RR 2.16, d=0.45). MET/CBT group had significantly lower baseline levels of actual help seeking than the control group (mean 0.3 vs 0.8).	Follow-up rate MET/CBT 52%, Control 47%
Important Outcomes				
Readiness to change	N/A	Meta-analysis: Smedslund 2011[9] (Not assessed)	NSD between **MI** and **No intervention** in 5 studies (n=1495, p=0.52; I^2=48%, p=0.10) • Brown 2010 (n=184 problem drinkers) • Carroll 2006a (n=423 substance use disorder) • Emmen 2005 (n=123 problem drinkers) • Freyer-Adam 2008 (n=595 problem drinkers) • Schaus 2009 (n=363 high-risk drinkers)	Alcohol/cannabis use

			NSD between **MI** and **Other** active intervention in 2 studies (n=350, p=0.78; I^2=0%, p=0.89) • Barnett 2007 (n=225 problem drinkers) • Kadden 2007 (n=240 cannabis use disorder)	
		RCT: Tait 2015[8]	Greater proportion of **MET/CBT** group transitioned to the action stage than **Control** group (n=160 ATS use, OR 4.13, 95% CI 1.03-16.58).	Follow-up rate MET/CBT 52%, Control 47%
		RCT: McCambridge & Strang 2004[10], 2005[11]	More **MI** participants reported increasing one motivational stage of change for drug use at 3 months than **TAU** group after controlling for baseline stage (n=200 adolescent/young adult stimulant [23%]/cannabis use, B = 0.76, p=0.004).	
		Pre-post: Smout 2010[3]	NSD after **Psychostimulant Check-Up** in proportion of participants in each stage of change (n=80 psychostimulant use).	Follow-up rate 62%
Acceptability	N/A	Prospective observation: Gerdtz 2020[12]	Most ER patients (85.6%, 95% CI 77.2- 91.2) accepted a **referral** to the alcohol and other drug clinician (n=457 ATS use).	

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Health care utilization	N/A	Meta-analysis: Bray 2011[1] (Not assessed)	29 studies (25 RCTs) of alcohol screening and brief interventions targeting non-alcohol-dependent populations in primary care, ED, and non-ED hospital settings. **No significant effect** of alcohol screening and brief interventions on outpatient health care utilization (follow-up range 6-120 months). Moderate heterogeneity (I-squared=53%, p=0.028). **No significant effect** of alcohol screening and brief interventions on ED utilization (follow-up range 6-120 months). No significant heterogeneity (I-squared = 14%, p=0.326) **No significant effect** of alcohol screening and brief interventions on inpatient health care utilization (follow-up range 6-120 months). Moderate to high heterogeneity (I-squared=69.7%, p=0.001). Inpatient care included any non-ED hospital stay or admission or inpatient treatment facility stay. AUD treatment not specified.	Alcohol use

SUD treatment utilization	N/A	Meta-analysis: Glass 2015[4] (Not assessed)	13 RCTs of brief alcohol interventions in general health-care settings with adult and adolescents were identified and 9 were included in the meta-analysis. **No significant effect** of brief alcohol intervention on subsequent alcohol treatment initiation (n=1930). No evidence of study heterogeneity. No significant effect for subgroup analyses which pooled results for adult, adolescent, high-severity, or low risk of bias studies.	Alcohol use
Important Outcomes				
Readiness to change	N/A	Meta-analysis: Smedslund 2011[9] (Not assessed)	59 RCTs of MI or MET for substance abuse among people with substance abuse or dependence. **NSD** between MI vs No intervention in 5 studies (n=1495, p=0.52; I^2=48%, p=0.10) • Brown 2010 (n=184 problem drinkers) • Carroll 2006a (n=423 substance use disorder) • Emmen 2005 (n=123 problem drinkers) • Freyer-Adam 2008 (n=595 problem drinkers) • Schaus 2009 (n=363 high-risk drinkers) **NSD** between MI vs Other active intervention in 2 studies (n=350, p=0.78; I^2=0%, p=0.89) • Barnett 2007 (n=225 problem drinkers) • Kadden 2007 (n=240 cannabis use disorder)	Alcohol/cannabis use

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Bernstein 2005[7]	RCT 6-mo follow-up USA Primary care	**(1) MI**: One motivational interview session (10-45 min) with a peer interventionist including active referral & referral handout followed in 10 days by one 5-10 min telephone booster call **(2) Control**: Referral handout	N=1175 adults recruited at primary care reporting last 30-day cocaine/heroin use (93% cocaine) and DAST10 score ≥ 3 (moderate-to severe problems related to drug use).	NSD in follow-up rate (83%, 81%) **Treatment system contact**: NSD among participants abstinent at 6 months (39% vs 37%). **Other outcomes**: Cocaine use, Addiction severity	In Patnode 2020a[13] Quality rating: Good Also in EtDT Prev SBI, EtDT Prev MI-BI
Gerdtz 2020[12]	Prospective observation	Harm reduction advice and referral	N=457 (59% male) patients admitted to a behavioral	**Referral acceptability:** Most patients accepted a referral to the	Also see EtDT Prev SBI

	Australia ER		assessment unit within an emergency department who tested positive or self-reported amphetamine-type stimulant use	alcohol and other drug clinician (85.6%, 95% CI 77.2- 91.2).	
Karno 2021[5]	RCT Study period: June 2013 to mid-2017 USA Outpatient (6 sites) & Inpatient (1 site)	**(1) SBIRT:** Single face-to-face session assessment with the ASSIST and BI tailored to ASSIST risk score. **(2) Control**: Health Education session (mean duration 20.3 minutes).	N= 718 adults seeking mental health treatment at one of 2 sites, with an affective or psychotic disorder diagnosis and reported any use of stimulants, cannabis, or a heavy drinking day in the past 90 days. Excluded if received treatment for a SUD in the previous 90 days. 34.3% reported stimulant use in the prior 90 days. 52.4% of sample exceeded threshold indicating severe mental illness (Kessler-6 score ≥ 13). (49.2% female, 47% non-white)	**Treatment access:** NSD in utilization of addiction treatment services for receipt of any service within 30 days of intervention (21.3% vs 24.3%) or total number of services received. **Other outcomes**: Stimulant use	Statistical analysis for stimulant sub-group not determined a priori, so results are exploratory only. Also see EtDT Prev SBI
Kim 2017[14]	RCT	brief intervention for drug use		Receipt of addiction treatment	
Marsden 2006[15]	RCT 6 mo follow-up UK Community	**(1) BI**: Self-assessment and single in-person motivational intervention session for 45-60 mins, manual guided, plus printed health risk information **(2) Control:** Self-assessment and printed health-risk information only	N=342 adolescents and young adults aged 16-22 yrs with **problematic** (at least four times over the past month) MDMA or cocaine use. Recruited via community advertising, outreach contact, and peer referral.	**Treatment utilization**: Engagement with treatment and other support services "not reported here" **Other outcomes**: NSD in stimulant abstinence, stimulant use frequency, stimulant use amount	In Li 2016[16] and Patnode 2020a[13] Quality rating: Good Also see EtDT Adol BI-MI, EtDT Prev SBI, EtDT Prev MI-BI
McCambridge & Strang 2004[10], 2005[11]	Cluster RCT 3, 12 mo follow-up UK Further education colleges	**(1) MI**: Single session (1 hour) in-person adapted from Miller & Rollnick 1991 and Rollnick 1992 **(2) TAU:** Usual education	N=200 adolescents and young adults aged 16-20 yrs with **weekly cannabis use or stimulant use** within the previous 3 months. Recruited by peer interviewers identified by school staff. Baseline stimulant use 23%. **At-risk population.**	89.5% followed up **Readiness to change**: More MI participants reported increasing one motivational stage of change in relation to drug use higher than control group at 3 months after controlling for baseline stage (B = 0.76, p=0.004).	In Li 2016[16] and Patnode 2020a[13] Quality rating: Fair Also see EtDT Adol BI-MI, EtDT Prev SBI,

				Other outcomes: Stimulant use, Drug-associated problems	EtDT Prev MI-BI
Poblete 2017[17]	Primary care, ED, police station	**(1) Brief intervention:** One 18 min brief individual counseling session based on FRAMES. **(2) Usual care**	12% received a cocaine-related brief intervention		Patnode 2020 (AHRQ) guideline Also see EtDT Prev SBI
Saitz 2014[2]	RCT June 2009-Jan 2012 6-mo follow-up USA Primary Care	**(1) BNI:** Brief negotiated interview, a 10- to 15-minute structured interview conducted by health educators **(2) MI:** Adaptation of Motivational Interviewing, a 30- to 45-minute intervention based on motivational interviewing with a 20- to 30-minute booster conducted by master's-level counselors **(3) No BI:** All participants received a list of SUD treatment and mutual help resources.	N=528 adult with drug use ASSIST substance-specific scores ≥4 at an urban hospital-based primary care internal medicine practice. Baseline 19% reported cocaine as main drug.	**Mutual help meeting attendance**: NSD **Hospitalizations and ED visits**: NSD **Health care utilization for addiction or mental health reasons**: NSD **Other outcomes:** Cocaine use, Cocaine use severity (ASSIST), Drug use consequences, Unsafe sex, Injection drug use	Also see EtDT Prev SBI, EtDT Prev Edu IDU
Smout 2010[3]	Pre-post 3-month follow-up Australia Community	**Psychostimulant Check-Up:** Single-session brief intervention for stimulant users	N=80 adults (39% female) who used psychostimulants (**98% injected MA as usual route of administration**) in the previous month recruited though community advertisements and fliers. A majority of participants (55) were in the 'action' stage of readiness to change at baseline.	Follow-up rate 62% **Treatment engagement**: NSD in number of health service contacts in last month (2 vs 1.9, p=0.813) **Readiness to change**: NSD in proportion of participants in each stage **Other outcomes**: Significant effects for MA use, MA-related negative consequences, Injection use, Patient satisfaction	Also see EtDT Prev SBI, EtDT Prev MI-BI, EtDT Prev Edu IDU
Stein 2009[6]	RCT 6-mo follow-up	**(1) Assessment + MI:** 4 sessions (each 20-40 min) of in-person MI to reduce	N=198 adults with regular cocaine use (at least weekly in past 6 months) recruited via advertisements in the community	Follow-up rate 81% **SUD treatment access**: NSD in any drug treatment (17.5% vs 19.8%, p=0.68)	In Patnode 2020a[13] Quality rating: Fair

	USA Community	cocaine use delivered by a therapist (n=97) **(2) Assessment + Control:** Written handout of treatment resources (n=101)	(38% female, 40% white). Current injection drug use: 23.5%. **Not screen-detected.**	**Other outcomes**: Favorable effect for reduced cocaine use frequency among heavy baseline users (≥15 out of 30 days); NSD for cocaine abstinence, SF-12 MCS, SF-12 PCS, and days employed (data NR)	Also see EtDT Prev MI-BI
Tait 2015[8]	RCT 6 mo follow-up Australia Home	**(1) MET+CBT**: 3 sessions of computer delivered MET/CBT **(2) Control**: Wait-list	N=160 out-of-treatment young adults (mean age 22.4 (SD 6.3) years) self-reporting use of ATS in the previous 3 months recruited via social network sites and posters in local clinics (75.6% male).	NSD in follow-up between groups at 6 months (52% % 47%). **Actual help seeking** (Actual Help-Seeking Questionnaire): Increased for intervention group, declined for control at 6 months (RR 2.16, d=0.45). Intervention group had significantly lower baseline levels of actual help seeking than the control group (mean 0.3 vs 0.8). **Help-seeking intentions** (General Help-Seeking Questionnaire): Increased for intervention group, declined for control at 6 months (RR=1.17; d=0.32). **Readiness to change:** Greater proportion of intervention group transitioned to the action stage than controls (OR 4.13, 95% CI 1.03-16.58). **Other outcomes:** NSD for ATS use, ATS risk, Quality of life (EUROHIS)	In Patnode 2020a[13] Quality rating: Fair Also see EtDT Adol BI-MI, EtDT Prev MI-BI

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016.
Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

World Health Organization. Technical Brief 4 on Amphetamine-Type Stimulants (ATS): Therapeutic interventions for Users of Amphetamine-Type Stimulants (ATS).; 2011.

Other Resources

Source	Resources	Comments
	Substance Abuse and Mental Health Services Administration. (2011). Screening, brief intervention and referral to treatment (SBIRT) in behavioral healthcare. Substance Abuse and Mental Health Services Administration.	
	Finding Quality Treatment for Substance Use Disorders (https://store.samhsa.gov/product/ PEP18-TREATMENT-LOC): This resource is for people seeking behavioral health services and treatment for SUDs. It provides guidance on how to fnd a quality treatment center and the steps to complete before accessing treatment.	
	TIP 35: Enhancing Motivation for Change in Substance Use Disorder Treatment (https:// store.samhsa.gov/product/PEP19-02-01-003): TIP 35 describes the elements of motivational interventions, the five principles of MI, catalysts for changing behavior, and the stages of change that clients go through while working toward recovery from SUDs	
	Smout M, Krasnikow S, Longo M, Wickes W, Minniti R, Cahill S. Quickfix: Identity & Intervene in Psychostimulant Use in Primary Health Care (Updated 2015). Drug and Alcohol Services South Australia; 2008. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/quickfix+identiy+intervene+in+psychostimulant+use+in+primary+health+care	

Evidence to Decision (EtD) Table:

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
1 RCT found a 1 hour counseling session increased readiness to change their cannabis or stimulant use, but it is not known if the intervention was directed at referral to treatment. NSD in treatment system contact in other RCTs. It is possible that the impact of referral to treatment is diluted by the relatively low prevalence of StUD and need for treatment in the study populations.	The benefits of offering treatment to those who need it is substantial, although this population will be small.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients may be uncomfortable receiving a referral to treatment.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
MA and SR interventions blended RT and clinical interventions where the goal was treatment entry (ie, extended duration sessions, multiple session interventions)		☐ No evidence ☒ Very low ☐ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		

Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Gerdtz (2020)[12]	Referral incurs a short-term time cost for clinicians. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Referral incurs a short-term time cost for clinicians. Highly variable by clinician and setting. Clinicians must be knowledgeable and up to date regarding local treatment options. Highly variable by clinician and setting.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion:

Justification

The benefits of offering treatment to those who need it is substantial, although this population will be small.

Subgroup Considerations

None noted

Implementation Considerations

Clinicians must be knowledgeable and up to date regarding local treatment options

References

1. Bray JW, Cowell AJ, Hinde JM. A systematic review and meta-analysis of health care utilization outcomes in alcohol screening and brief intervention trials. *Med Care*. 2011;49(3):287-294. doi:10.1097/MLR.0b013e318203624f
2. Saitz R, Palfai TPA, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513. doi:10.1001/jama.2014.7862
3. Smout M, Longo M, Harrison S, et al. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. *Drug Alcohol Rev*. 2010;29(2):169-176. doi:10.1111/j.1465-3362.2009.00133.x
4. Glass JE, Hamilton AM, Powell BJ, Perron BE, Brown RT, Ilgen MA. Specialty substance use disorder services following brief alcohol intervention: a meta-analysis of randomized controlled trials. *Addict Abingdon Engl*. 2015;110(9):1404-1415. doi:10.1111/add.12950
5. Karno MP, Rawson R, Rogers B, et al. Effect of screening, brief intervention and referral to treatment for unhealthy alcohol and other drug use in mental health treatment settings: a randomized controlled trial. *Addict Abingdon Engl*. 2021;116(1):159-169. doi:10/gn756x
6. Stein MD, Herman DS, Anderson BJ. A motivational intervention trial to reduce cocaine use. *J Subst Abuse Treat*. 2009;36(1):118-125. doi:10.1016/j.jsat.2008.05.003
7. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend*. 2005;77(1):49-59. doi:10.1016/j.drugalcdep.2004.07.006
8. Tait RJ, McKetin R, Kay-Lambkin F, et al. Six-Month Outcomes of a Web-Based Intervention for Users of Amphetamine-Type Stimulants: Randomized Controlled Trial. *J Med Internet Res*. 2015;17(4):e105. doi:10/gn763w
9. Smedslund G, Berg RC, Hammerstrøm KT, et al. Motivational interviewing for substance abuse. *Campbell Syst Rev*. 2011;7(1):1-126. doi:10.4073/csr.2011.6
10. McCambridge J, Strang J. The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial. *Addiction*. 2004;99(1):39-52. doi:10.1111/j.1360-0443.2004.00564.x
11. McCambridge J, Strang J. Deterioration over time in effect of Motivational Interviewing in reducing drug consumption and related risk among young people. *Addiction*. 2005;100(4):470-478. doi:10.1111/j.1360-0443.2005.01013.x
12. Gerdtz M, Yap CYL, Daniel C, et al. Amphetamine-type stimulant use among patients admitted to the emergency department behavioural assessment unit: Screening and referral outcomes. *Int J Ment Health Nurs*. 2020;29(5):796-807. doi:10.1111/inm.12710
13. Patnode CD, Perdue LA, Rushkin M, et al. Screening for Unhealthy Drug Use: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;323(22):2310. doi:10.1001/jama.2019.21381
14. Kim TW, Bernstein J, Cheng DM, et al. Receipt of addiction treatment as a consequence of a brief intervention for drug use in primary care: a randomized trial. *Addict Abingdon Engl*. 2017;112(5):818-827. doi:10.1111/add.13701
15. Marsden J, Stillwell G, Barlow H, et al. An evaluation of a brief motivational intervention among young ecstasy and cocaine users: no effect on substance and alcohol use outcomes. *Addiction*. 2006;101(7):1014-1026. doi:10.1111/j.1360-0443.2006.01290.x
16. Li L, Zhu S, Tse N, Tse S, Wong P. Effectiveness of motivational interviewing to reduce illicit drug use in adolescents: a systematic review and meta-analysis. *Addiction*. 2016;111(5):795-805. doi:10.1111/add.13285
17. Poblete F, Barticevic NA, Zuzulich MS, et al. A randomized controlled trial of a brief intervention for alcohol and drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in primary health care in Chile: ASSIST-BI for alcohol and drugs in Chile. *Addiction*. 2017;112(8):1462-1469. doi:10.1111/add.13808

Table 55. Early Intervention Peer Navigation

Recommendation: Clinicians should consider the use of peer navigators to link patients to StUD assessment and treatment.

Clinical Question Summary Table

Clinical Question	Does peer navigation improve referral for treatment in patients with a positive screen?
Population	Patients with StUD use being referred for StUD assessment and treatment
Intervention	Peer navigators
Comparison	TAU
Main Outcomes	Engagement in treatment
Setting	Outpatient settings or harm reduction settings
Background & Definitions	Background information on the question, more detailed description of the interventions Notes: • Peer support specialists for recovery priming (Stanojlovic 2021)[1] • Peer support specialists for Recovery Initiation and Stabilization, Engagement in Care, Treatment Initiation, and Retention (Stanojlovic 2021)[1] (Also in Prev BI-Referral)
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA**: Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder, **TAU**: Treatment as usual
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
HIV	N/A	Seamaan 2002[2]	Semaan S, Des Jarlais DC, Sogolow E, Johnson WD, Hedges LV, Ramirez G. A meta-analysis of the effect of HIV prevention interventions on the sex behaviors of drug users in the United States. *J Acquir Immune Defic Syndr*. 2002;30(Suppl 1):S73–93.	

		Bouzanis 2021[3]	• Jozaghi 2014 (Cohort, crack cocaine/MA smokers in Canada, peer delivered counselling and testing) Reduced risk of contracting an infectious disease such as HIV, HCV, and TB Qualitative, peer delivered counselling and testing, Canada • Markwick N, Ti L, Callon C, et al. Willingness to engage in peer delivered HIV voluntary counselling and testing among people who inject drugs in a Canadian setting. *J Epidemiol Community Health*. 2014;68:675-678.10.1136/jech-2013-203707 Qualitative, peer-delivered injections, Canada • McNeil R, Small W, Lampkin H, et al. "People knew they could come here to get help": an ethnographic study of assisted injection practices at a peer-run 'unsanctioned' supervised drug consumption room in a Canadian setting. *AIDS Behav*. 2014;18:473-485.10.1007/s10461-013-0540-y	
Injection risk behavior	N/A	Meta-analysis: Medley 2009[4]	Peer education interventions for HIV prevention among PWID in developing countries (including 'upper-middle income countries'). **Peer education interventions** associated with significant reduction in equipment sharing among PWID across 4 studies (2 cohort, 2cross-sectional studies) (k=6, 3240 participants, OR=0.37 [0.20, 0.67]). Significant heterogeneity. • Positive association found: Broadhead 2006; Hammett 2006; Sergeyev 1999) • No association found: Li, Luo, & Yang, 2001	
Linkage to HCV care	N/A	Systematic review: Schwarz 2022[5] (not appraised)	Studies reporting on linkage to care interventions aimed to increase the likelihood of PWID visiting a provider/specialist after having tested positive for HCV for an initial evaluation in order to start treatment. Peer support: • "Peer involvement interventions showed a positive but not significant effect on linkage to care and adherence to treatment, based on the results retrieved. However, peer support is widely acknowledged in HCV elimination, in particular when addressing and engaging hard-to-reach populations such as PWID in the care cascade (WHO, 2018)." (p 12) • Broad 2020 (RCT, n=380 peer-recruited IDUs, POC HCV testing by peers vs Testing as usual) NSD in HCV treatment initiation within 6 months. However, 61% had no history of past HCV testing.	

			• Ward 2019 (RCT, n=90 outpatient SUD w/ HIV+, Peer mentors vs Usual care) NSD in HCV treatment initiation (83% vs 67%)	
Important Outcomes				
HCV incidence	N/A	Sacks-Davis 2012[6]	Peer-educator training for preventing hepatitis C infection in adults who inject drug HCV vs Non-participants	
		Bouzanis 2021[3]	Cohort, peer delivered counselling and testing, Canada • Jozaghi E. The role of drug users' advocacy group in changing the dynamics of life in the Downtown Eastside of Vancouver, Canada. J Subst Use 2014;19:213–8. Qualitative, peer-delivered injections, Canada • McNeil R, Small W, Lampkin H, et al. "People knew they could come here to get help": an ethnographic study of assisted injection practices at a peer-run 'unsanctioned' supervised drug consumption room in a Canadian setting. *AIDS Behav*. 2014;18:473-485.10.1007/s10461-013-0540-y	
Risky sexual behavior	N/A	Systematic review: Fischer 2015[7] (Not assessed)	Positive effect of **peer-delivered HIV-risk reduction interventions** for crack cocaine users on sexual risk behavior**:** • Weeks 2009 (longitudinal cohort, n=523 IDU and/or inhalers [majority crack], peer-led 'Risk Avoidance Partnership') **Intervention favored** in sexual risk outcomes at 6 months. • Cottler 1998 (RCT, n=725 out-of-tx crack users, peer-delivered 'EachOneTeachOne' vs NIDA Standard HIV Intervention) **Mixed**. Intervention favored in reduced number of sexual partners. NSD in condom use.	HIV interventions for people who use crack cocaine
		Schwarz 2022[5] Fischer 2015[7] Chan 2022[8] Rigoni 2018[9]	24 HIV prevention interventions for GBMSM were included strongly recommended for implementation in Europe: peer out-reach (providing information and peer support), peer-led group interventions (interactive group activities where a trained peer facilitates promotion of precautionary behaviours for HIV)	European context
		Meta-analysis: Medley 2009[4]	Peer education interventions for HIV prevention among PWID in developing countries (including 'upper-middle income countries'). **Peer education interventions** associated with significant increase in condom use among PWID (k=3, OR=1.49 [1.05, 2.10], p<0.05). Significant heterogeneity.	Effectiveness of peer education interventions for HIV prevention in developing countries

Drug use	N/A	Tanner-Smith 2022[10]	9 studies of drug-targeted Bis delivered by peer interventionists • drug-targeted BIs yielded larger improvements in multiple drug/mixed substance use outcomes when delivered by a general practitioner (g = 0.19, 95% CI = 0.187, 0.193) compared to other interventionists (g = 0.05, 95% CI = −0.88, 0.97 for peer providers). • drug-targeted BIs were associated with significantly worse (ie higher) levels of substance use consequences when delivered by a primary care provider (g = − 0.05, 95% CI = −0.06, −0.049) compared to other interventionists (g = 0.11, 95% CI = −0.27, 0.49 for peer providers)	
		Systematic review: Fischer 2015[7] (Not assessed)	Positive effect of **peer-delivered HIV-risk reduction interventions** for crack cocaine users on drug use: • Weeks 2009 (longitudinal cohort, n=523 IDU and/or inhalers [majority crack], peer-led 'Risk Avoidance Partnership') **Intervention favored** for drug use at 6 months. • Cottler 1998 (RCT, n=725 out-of-tx crack users, peer-delivered 'EachOneTeachOne' vs NIDA Standard HIV Intervention) **Intervention favored** in reducing crack use. • Schlosser 2008 (RCT, n=923 out-of-treatment crack users, peer-delivered HIV intervention vs NIDA Standard HIV Intervention) **Intervention favored for** crack use at 3 months.	HIV interventions for people who use crack cocaine

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Burgess 2018[11]					In Rigoni 2018[9]
Latkin 1998[12]					In Rigoni 2018[9] & MacArthur 2014[13]
Latkin 2003[14]					In Copenhaver 2006[15] & MacArthur 2014[13]
Lyons 2014[16]		"C-TALK" intervention; 10 small-group sessions of 1.5 hr	Men who reported using stimulants before or during	At 12-week followup (postenrolment): * Significant	In Knight 2019[17]

		each, led by either MSM peers who were former stimulant users (two facilitators)	condomless anal intercourse in the previous 6 months	declines were seen between baseline and follow-up in both meth use ($P < 0.001$) and intervention * The modified GCBT brought about greater reductions in the number of male sexual partners, but all GCBT conditions reduced CAI at similar levels.	
Samuels 2019[18]	ED	Lifespan Opioid Overdose Prevention (LOOP (program) provided ED patients at risk of opioid overdose. They utilised: 1) intranasal THN and overdose rescue education 2) recovery coach consultation for addiction		ED naloxone distribution and consultation of a community-based peer recovery coach were feasible, acceptable and maintained over time. Post implementation, provision of THN naloxone increased from none to 35 % ($p < 0.001$), consultations with a recovery coach from none to 33 % ($p < 0.001$), and discharge with referral to treatment increased from 9% to 21% ($p = 0.003$). Rates of THN provision and recovery coach consultations appeared to be maintained 12 months after program implementation.	
Sherman 2009[19]	RCT 12 months Thailand	**(1)** Peer-education network intervention 7 sessions targeted stimulant use (primary) and sexual risk (secondary) **(2)** Life-skills curriculum	N=983 young MA users (at least three times in the past 3 months) (74% male)	Retention 90% at 3 months **MA use** (self-report): NSD between groups. Significant decrease over time. **Condom use**: NSD between groups. Significant increase over time. **HIV incidence:** NSD between groups. **HCV incidence:** NSD between groups. **STI incidence**: NSD between groups.	In Colfax 2010[20] Also see EtDT Prev Edu Sex

Waye 2019[21]	ED	AnchorED provided on-call Peer Recovery Specialists for patients with opioid overdose treated at any of Rhode Island's 10 EDs; overdose prevention education and naloxone training in the ED; naloxone kit to people at risk of an opioid overdose. 20−30 min; Peer Recovery Specialists	patients with opioid overdose treated at any of Rhode Island's 10 EDs	AnchorED had high engagement rates and connected high-risk individuals to necessary resources, including overdose prevention education, naloxone training and distribution, as well as peer recovery counselling services. Among the 1329 AnchorED contacts, 89 % received naloxone training, 87 % agreed to postED engagement with a Peer Recovery Specialist, and 51 % agreed to service referrals.	

Evidence-Based Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[8]	Harm Reduction in Health Care Settings Injection-Related Practices (p. 203) • "Injecting drugs is a multistep process, and clinicians should be knowledgeable on safer injection practices to counsel their patients on approaches to decrease their risk of infections. **Peer educators**, defined as individuals with lived experience using substances, or who share other common characteristics/experiences with the person they are educating, may be another option if clinicians are not comfortable providing this counseling." (Chan et al., 2022, p. 203)	
Rigoni 2018[9]	Speed Limits: Harm Reduction for People Who use Stimulants • "Peer-based models are an important mechanism to put harm reduction interventions into practice, especially for out of hours provision of services (IDPC 2016)." (Rigoni et al., 2018, p. 9) • "Evidence shows that peer education – in a supportive non-stigmatising and non-incriminating environment – is the most effective way to share new knowledge and skills among PWUD." (Rigoni et al., 2018, p. 38) • "Peer outreach is particularly effective for safer drug use education and distribution of paraphernalia (Jozaghi 2014)." (Rigoni et al., 2018, p. 38)	

	• "Outreach work can also support PWUS to avoid starting injecting or encourage people who inject to transit to non-injection routes of administration. This can be done through informing people about the risks of injecting or about safer methods to use (Pinkham and Stone 2015; United Nations Office on Drugs and Crime 2017)." (Rigoni et al., 2018, p. 38)	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Some extrapolation. safe consumption, HCV and BI stronger compared to primary care (BIs)		☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Undesirable effects of peer encounter none to small.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Substantially favors intervention	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Varies some. Some extrapolation. Safe consumption, HCV and BI stronger compared to primary care (BIs)	Generally low to moderate most not specifically related to StUD but some (crack cocaine) safe consumption sites (some)	☐ No evidence ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on level of care and space, integrating peers into treatment can be issue in EDs, hospital, COVID19 visitation issues, other. Peer reimbursement (volunteer vs paid),	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Peers have higher credibility than others in health care, able to fluidly interact with individuals with StUD outside of traditional types of encounters.

Subgroup Considerations

None noted

Implementation Considerations

Feasibility, models of peer integration (in particular in ED/hospital levels of care outside of some of the standard addiction treatment infrastructure).

References

1. Stanojlović M, Davidson L. Targeting the Barriers in the Substance Use Disorder Continuum of Care With Peer Recovery Support. *Subst Abuse*. 2021;15:1178221820976988. doi:10.1177/1178221820976988
2. Semaan S, Des Jarlais DC, Sogolow E, Johnson WD, Hedges LV, Ramirez G. A meta-analysis of the effect of HIV prevention interventions on the sex behaviors of drug users in the United States. *J Acquir Immune Defic Syndr*. 2002;30(Suppl 1):S73-93.
3. Bouzanis K, Joshi S, Lokker C, et al. Health programmes and services addressing the prevention and management of infectious diseases in people who inject drugs in Canada: a systematic integrative review. *BMJ Open*. 2021;11(9):e047511. doi:10.1136/bmjopen-2020-047511
4. Medley A, Kennedy C, O'Reilly K, Sweat M. Effectiveness of Peer Education Interventions for HIV Prevention in Developing Countries: A Systematic Review and Meta-Analysis. *AIDS Education and Prevention*. 2009;21(3):181-206. doi:10.1521/aeap.2009.21.3.181
5. Schwarz T, Horváth I, Fenz L, Schmutterer I, Rosian-Schikuta I, Mårdh O. Interventions to increase linkage to care and adherence to treatment for hepatitis C among people who inject drugs: A systematic review and practical considerations from an expert panel consultation. *Int J Drug Policy*. 2022;102:103588. doi:10.1016/j.drugpo.2022.103588
6. Sacks-Davis R, Horyniak D, Grebely J, Hellard M. Behavioural interventions for preventing hepatitis C infection in people who inject drugs: A global systematic review. *Int J Drug Policy*. 2012;23(3):176-184. doi:10.1016/j.drugpo.2011.08.002
7. Fischer B, Blanken P, Da Silveira D, et al. Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: a comprehensive narrative overview of English-language studies. *Int J Drug Policy*. 2015;26(4):352-363. doi:10/f66rht
8. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

9. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
10. Tanner-Smith EE, Parr NJ, Schweer-Collins M, Saitz R. Effects of brief substance use interventions delivered in general medical settings: a systematic review and meta-analysis. *Addiction*. 2022;117(4):877-889. doi:10.1111/add.15674
11. Burgess K, Parkhill G, Wiggins J, Ruth S, Stoovè M. Re-Wired: treatment and peer support for men who have sex with men who use methamphetamine. *Sex Health*. 2018;15(2):157. doi:10.1071/SH17148
12. Latkin CA. Outreach in natural settings: the use of peer leaders for HIV prevention among injecting drug users' networks. *Public Health Rep*. 1998;113 Suppl 1(Suppl 1):151-159.
13. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *Int J Drug Policy*. 2014;25(1):34-52. doi:10.1016/j.drugpo.2013.07.001
14. Latkin CA, Sherman S, Knowlton A. HIV prevention among drug users: Outcome of a network-oriented peer outreach intervention. *Health Psychol*. 2003;22(4):332-339. doi:10.1037/0278-6133.22.4.332
15. Copenhaver MM, Johnson BT, Lee IC, Harman JJ, Carey MP. Behavioral HIV risk reduction among people who inject drugs: Meta-analytic evidence of efficacy. *Journal of Substance Abuse Treatment*. 2006;31(2):163-171. doi:10.1016/j.jsat.2006.04.002
16. Lyons T, Tilmon S, Fontaine YM. Development of a Small-Group Intervention for Stimulant-Using Men Who Have Sex With Men. *J Groups Addict Recover*. 2014;9(1):54-70. doi:10.1080/1556035X.2014.868724
17. Knight R, Karamouzian M, Carson A, et al. Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine: A systematic review. *Drug and Alcohol Dependence*. 2019;194:410-429. doi:10.1016/j.drugalcdep.2018.09.023
18. Samuels EA, Baird J, Yang ES, Mello MJ. Adoption and Utilization of an Emergency Department Naloxone Distribution and Peer Recovery Coach Consultation Program. Hwang U, ed. *Acad Emerg Med*. Published online October 3, 2018:acem.13545. doi:10.1111/acem.13545
19. Sherman SG, Sutcliffe C, Srirojn B, Latkin CA, Aramratanna A, Celentano DD. Evaluation of a peer network intervention trial among young methamphetamine users in Chiang Mai, Thailand. *Soc Sci Med*. 2009;68(1):69-79. doi:10.1016/j.socscimed.2008.09.061
20. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *The Lancet*. 2010;376(9739):458-474. doi:10.1016/S0140-6736(10)60753-2
21. Waye KM, Goyer J, Dettor D, et al. Implementing peer recovery services for overdose prevention in Rhode Island: An examination of two outreach-based approaches. *Addict Behav*. 2019;89:85-91. doi:10.1016/j.addbeh.2018.09.027

Harm Reduction

Table 56. Education Stimulants

Recommendation: For patients who engage in risky stimulant use, clinicians should:

a. offer basic harm reduction education about safer stimulant use,
b. tailor harm reduction education to the patient's patterns of substance use (eg, context of their use, route of administration, and type of preparation).

Clinical Question Summary:

Clinical Question	What are effective educational strategies for reducing harms related to stimulant use or StUD-related behaviors?
Population	People who engage in risky stimulant use
Intervention	Harm reduction education about safer stimulant use
Comparison	No education
Main Outcomes	Harm reduction related outcomes
Setting	Outpatient or Harm Reduction settings
Background & Definitions	Notes: • Long-term health consequences associated with stimulant use o Commentary. "From a public health perspective, efforts to educate MA-using youth about the long-term health outcomes associated with MA use are critical to reduce such risks [4]. In general, research supports the effectiveness of increasing the risk perceptions about long-term disease outcomes among this age group [youth], especially in tobacco and HIV-related prevention work [5,6]" (Rawson & Gonzales, 2010, p1)[1] • Increased risk of harm associated with homemade drugs o "As the consequences of injecting these homemade substances are considerably more acute than existing illicit narcotics [26], and life expectancy lower [19], treatment providers globally should be cognizant of the dangers of, presentation, and harms related to homemade drug use." (Hearne 2016, p2)[2] o "Countries outside of Eastern Europe should be well informed about these grave public health concerns. A variety of opioid and stimulant syntheses are described in detail on the Internet, and the precursors and reactants are readily available." (Hearne 2016, p8)[2] o in people who inject homemade (meth)cathinone (boltushka), "overexposure to manganese is a severe condition that can become manifest after only a few months of boltushka injecting, with symptoms of dysarthria, hypokinesia, dystonia, and damaged posture [113–115]. Boltushka synthesis includes the oxidation of (the precursor) with permanganate or "marganzovka", a commonly used disinfectant in Russia, in water [44]. During the reaction, Manganese (Mn) is released and toxic levels of remnants remain in the liquid drug… the resulting Parkinsonism syndrome is not reversible [44]. Studies suggest Manganism related to (meth)cathinone injection amongst immigrants in Western Europe and in Canada [116]" (Hearne 2016, p7)[2]

	○ "Another risk is caused by improper synthetisation of stimulants – for instance when they are home produced. Stimulants may contain toxic chemical residues or other impurities. Some of these impurities are associated with high levels of morbidity and many complex health issues such as the spread of blood borne viruses, gangrene, and internal organ damage, as well as with cognitive defects, dementia-like memory issues, gangrene haemorrhage and parkinsonism (Grund et al. 2010; Hearne et al. 2016)." (Rigoni 2018, p19)[3] • ATS use was associated with an increased risk of stroke/myocardial infarction in one review (Lappin, 2017); Farrell 2019[4] identified this as level C (Findings across cohorts of drug users) evidence. • Cocaine use was associated with an increased risk of stroke/myocardial infarction (aOR: 13.9 [1.48 to 9.4]) in one review (Sordo 2014)[5]; Farrell 2019[4] identified this as level C (findings across cohorts of drug users) evidence. • ATS use was associated with an increased risk of respiratory/lung disease associated with ATS use in one review (Pilowsky 2011); Farrell 2019[4] identified this as level C (findings across cohorts of drug users) evidence. • Cocaine use was associated with an increased risk of hospitalization for asthma associated with cocaine use in one review (Butler 2017)[6]. Farrell et al (2019)[4] identified this as level C (findings across cohorts of drug users) evidence.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/ Important Outcomes				
Harm Reduction	N/A	Review of reviews: Farrell 2019[4] (Not assessed)	"Harm reduction approaches to reducing risky stimulant use and the harms of acute intoxication are not well evaluated. Common strategies include providing information and education about avoiding rapid-onset routes of administration (such as smoking and injecting), limiting the quantity and frequency of stimulant use, identifying early signs of stimulant psychosis (eg, illusions and persecutory ideation), general advice on risk assessment (eg, drug driving), and tips on general health (eg, sleep hygiene, diet, and dental health)."	Interventions to reduce stimulant related harms

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Carrico 2014[7]	Pre-post 1-year program Trial 1: 12-month assessment Trial 2: 6-month assessment USA Community/ Outpatient	**The Stonewall Project**: Integrated harm reduction and treatment model. Includes HR interventions (safe use, safe injection, sexual risk-reduction education) and weekly individual and twice weekly group Matrix Model-based outpatient treatment sessions. strategies for patients to: (1) transition to less potent modes of MA administration (eg, injecting to smoking, smoking to snorting); (2) promoting self-care strategies while using MA; and (3) delivering education about safer injection	N=211 MSM who use **MA** *Trial 1:* N=123 (66% white, 64% HIV+, 44% on ART) *Trial 2:* N=88 (67% white, 66% HIV+, 86% on ART)	*Trial 1: n*=112 (91%) completed at least one follow-up assessment **Cocaine/crack use** (ASI): Significant reductions in past 30 days of use at 12 months (incidence rate ratio [IRR]=0.54 [0.32, 0.91], p<0.005, *d*= -0.12, Δ expected= -46.3%) **MA use** (ASI): NSD **Undetectable HIV viral load**: More HIV-positive participants reported an undetectable viral load over the 12-month follow-up (OR=2.23 [1.12, 4.41], p<0.005, Cohen's *h*=0.38)	In Pantalone 2020[8] Also in EtDT Prev Edu IDU

		practices with linkage to needle exchanges and access to sterile syringes.		*Trial 2: n*=85 (96%) completed at least one follow-up assessment **Cocaine/crack use** (self-report): NSD **MA use** (self-report): Significant reductions in past 30-day use at 6 months (IRR=0.71 [0.52, 0.96], p<0.05, *d*= -0.24, Δ expected= -29.4%) **Sexual risk behavior (self-report):** NSD in any UAI at 6 months. Reduction in number of anal sex partners while using MA (IRR=0.45 [0.27, 0.73], p<0.01, *d*= -0.33, Δ expected= -55.1%). Reduction in unprotected receptive anal sex on MA (OR=0.53 [0.30, 0.94], p<0.001, Cohen's *h*= -0.24) **Undetectable HIV viral load**: NSD	
Radfar 2017[9]	Pre-post Sept 2014-March 2015 3-mo follow-up Iran drop in centers (DICs)	1-session (20-30 mins) MA harm reduction psychoeducation + weekly booster sessions integrated into opioid harm reduction services of 10 drop in centers (DICs)	N=357 (18.5% female) adults who used MA at least once/month in prior 3 months.	**Condom use**: Increased condom during last intercourse (p = 0.04). **Sex under influence of MA**: nsd at month 3 (p=0.2) **Knowledge**: Increased knowledge of MA harms and side effects (p= 0.001).	
Saitz 2014[10]	RCT June 2009-Jan 2012 6-mo follow-up USA Primary Care	**(1) BNI:** Brief negotiated interview, a 10- to 15-minute structured interview conducted by health educators **(2) MI:** Adaptation of Motivational Interviewing, a 30- to 45-minute intervention based on motivational	N=528 adult with drug use ASSIST substance-specific scores ≥4 at an urban hospital-based primary care internal medicine practice. Baseline 19% reported cocaine as main drug.	**Drug use consequences**: **Other outcomes:** Cocaine use, Cocaine use severity (ASSIST), Drug use consequences, Unsafe sex, Health care utilization, Injection drug use	Also see EtDT Prev SBI, EtDT Prev Refer to Tx

		interviewing with a 20- to 30-minute booster conducted by master's-level counselors **(3) No BI:** All participants received a list of SUD treatment and mutual help resources.			
Smout 2010[11]	Longitudinal cohort 3-month follow-up Australia Community	**Psychostimulant Check-Up**: Single-session brief intervention for stimulant users	N=80 adults (39% female) who used psychostimulants (**98% injected MA as usual route of administration**) in the previous month recruited though community advertisements and fliers. A majority of participants (55) were in the 'action' stage of readiness to change at baseline.	Follow-up rate 62% **MA-related negative consequences**: **Other outcomes**: MA use, Readiness to change, Treatment engagement, Patient satisfaction, Injection use	Also see EtDT Prev SBI, EtDt Prev Refer to Tx

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016.
Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.
Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004
United Nations Office on Drugs and Crime, World Health Organization (WHO), and Joint United Nations Programme on HIV/AIDS (UNAIDS). HIV prevention, treatment, care and support for people who use stimulant drugs; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf

Non-Systematic Reviews & Commentary

Source	Recommendations	Comments
Chan 2022[12]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE • "Overamping" is a term frequently used to describe the negative physical and psychological effects of stimulant use, akin to an overdose.65 This term is not well defined in the literature, and it can imply a wide range of symptoms (stimulant overdose can include cardiovascular collapse and/or death). (p. 210) Route of administration	

	• For people who use stimulants, clinicians should ask the route of delivery to further tailor HR counseling. • For individuals who use substances rectally, the goal is to prevent infections and to protect the skin from breakdown; we recommend that individuals mix the substance with sterile water, use lubrication, avoid sharing equipment, and use sterile equipment.	
Rigoni 2018[3]	Speed Limits: Harm Reduction for People Who use Stimulants	

Evidence to Decision (EtD) Table:

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
When ed is paired with other HR, evidence is strong for education + interventions for variety of outcomes	Stage of change may impact outcome, indiv already seeking treatment, active RTC may have better outcomes, be more receptive to education	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Good clinical practice. Educate about disease, follow through on implementation of practices	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison

		☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Education alone – low		☐ No evidence ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	May vary based on readiness to change	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		

Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on clinician knowledge and comfort	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusions:

Justification

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. Education is an important component of change and relatively easy to implement; the importance of patient education is readily supported across a range of other medical conditions.

Subgroup Considerations

Patients with high readiness to change may have better outcomes.

Implementation Considerations

Requires combining with other HR activities. Requires clinician knowledge and comfort with harm reduction principles

Research Priorities

- Studies needed in individuals not in active stage of change.
- Ways to reduce accidental overdose from potent synthetic opioids, either adulterated orused in conjunction with stimulants.
- Use of stimulants in safe consumption sites
- Long term health effects of smoking vs IDU

References

1. Rawson RA, Gonzales R. Commentary on Marshall et al. (2010):Are long-term negative health consequences of methamphetamine use important to youth? *Addict Abingdon Engl*. 2010;105(6):1003-1004. doi:10.1111/j.1360-0443.2010.02991.x
2. Hearne E, Grund JPC, Van Hout MC, McVeigh J. A scoping review of home-produced heroin and amphetamine-type stimulant substitutes: implications for prevention, treatment, and policy. *Harm Reduct J*. 2016;13(1):14. doi:10.1186/s12954-016-0105-2
3. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
4. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
5. Sordo L, Indave BI, Barrio G, Degenhardt L, de la Fuente L, Bravo MJ. Cocaine use and risk of stroke: A systematic review. *Drug Alcohol Depend*. 2014;142:1-13. doi:10.1016/j.drugalcdep.2014.06.041
6. Butler AJ, Rehm J, Fischer B. Health outcomes associated with crack-cocaine use: Systematic review and meta-analyses. *Drug Alcohol Depend*. 2017;180:401-416. doi:10.1016/j.drugalcdep.2017.08.036
7. Carrico AW, Flentje A, Gruber VA, et al. Community-Based Harm Reduction Substance Abuse Treatment with Methamphetamine-Using Men Who Have Sex with Men. *J Urban Health*. 2014;91(3):555-567. doi:10.1007/s11524-014-9870-y

8. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
9. Radfar SR, Mohsenifar S, Noroozi A. Integration of Methamphetamine Harm Reduction into Opioid Harm Reduction Services in Iran: Preliminary Results of a Pilot Study. *Iran J Psychiatry Behav Sci*. 2017;11(2). doi:10.5812/ijpbs.7730
10. Saitz R, Palfai TPA, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513. doi:10.1001/jama.2014.7862
11. Smout M, Longo M, Harrison S, et al. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. *Drug Alcohol Rev*. 2010;29(2):169-176. doi:10.1111/j.1465-3362.2009.00133.x
12. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 57. Prevention Refer to Harm Reduction

Recommendation:

1. For patients who engage in **risky stimulant use**, clinicians should: refer to relevant local harm reduction services as indicated based on the clinical assessment.
2. For patients who engage in **risky sexual behaviors**, clinicians should: consider offering a referral to a local psychosocial sex education program or harm reduction program that addresses risky sexual behavior for additional or continuing harm reduction intervention.

Clinical Question Summary Table

Clinical Question	Does referral for harm reduction services reduce harms related to stimulant use or StUD-related behaviors?
Population	People who engage in risky stimulant use
Intervention	Harm reduction education about risky sexual behaviors
Comparison	No education
Main Outcomes	Harm reduction related outcomes
Setting	Outpatient or Harm Reduction settings
Background & Definitions	According to the principles of harm reduction, clinicians can engage patients who use stimulants in treatment and prevention services, accounting for patients' desires and levels of interest, motivation, and engagement.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Toth 2016[1]	Cross-section Denmark Supervised consumption facility (SCF)	Self-reported receipt of education in hygienic injection practices at SCF	n=154 PWUD who used at least one of five SCFs; 10% < 30 years; 25% female	**Use of SCF to access clean injection equipment** (self-report yes vs. no): Those who had received education on hygienic injection practices at a SCF were more likely to access SCFs for clean injection equipment vs. those who had	In systematic review Kennedy 2017[2]

				not received such education (68.8 vs. 25.9%, p = 0.024).	

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016.
Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Evidence to Decision (EtD) Table:

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Expert guidance on referral to HR exists, but no strong direct evidence. Evidence that accessing these services has a substantial desirable effect on reducing harms from risky sexual behavior and injection drug use.	Avenue through which patients who use stimulants, IDU, risky sexual behavior, is through referral to programs to reduce the harms associated with such behaviors.	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients might be upset. HR programs are associated with poverty. Not all patients may feel comfortable accessing HR services.	☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Don't have good evidence on the clinical impact of referral, so confidence on the magnitude of the actual effect is very low.		☐ No evidence ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Historically, there was uncertainty, but there is increasing prioritization of HR services.	☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	These programs are often available for low income, uninsured, otherwise vulnerable population, so they will likely not experience significant barriers to accessing these services	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Historically, there was less acceptability due to stigma, but there is increasing acceptability of HR services.	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	These services tend to be accessible regardless of income and doesn't require a specialist provider, although accessibility may vary by region and depends on provider knowledge of local services.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

Expert guidance on referral to HR exists, but no strong direct evidence. Evidence that accessing these services has a substantial desirable effect on reducing harms from risky sexual behavior and injection drug use.

Subgroup Considerations

These programs are often available for low income, uninsured, otherwise vulnerable population, so they will likely not experience significant barriers to accessing these services

Implementation Considerations

- Clinicians will need to stay up to date on locally available services.

References

1. Toth EC, Tegner J, Lauridsen S, Kappel N. A cross-sectional national survey assessing self-reported drug intake behavior, contact with the primary sector and drug treatment among service users of Danish drug consumption rooms. *Harm Reduct J*. 2016;13(1):27. doi:10.1186/s12954-016-0115-0
2. Kennedy MC, Karamouzian M, Kerr T. Public Health and Public Order Outcomes Associated with Supervised Drug Consumption Facilities: a Systematic Review. *Curr HIV/AIDS Rep*. 2017;14(5):161-183. doi:10.1007/s11904-017-0363-y

Table 58. Education Overdose

Recommendation: For patients who engage in risky stimulant use, clinicians should: offer harm reduction education on overdose prevention and reversal.

Clinical Question: Summary Table

Clinical Question	What are effective strategies for preventing overdose in patients with StUD?
Population	People who engage in risky stimulant use
Intervention	Harm reduction education about overdose prevention and referral
Comparison	No education
Main Outcomes	Harm reduction related outcomes
Setting	Clinical settings
Background & Definitions	Background information on the question, more detailed description of the interventions Notes: • "Very high doses of stimulant drugs consumed in a short amount of time can trigger acute respiratory distress, chest pain, palpitations or myocardial infarctions [112]. In extreme cases this can result in cardiac arrest. The first signs of stimulant drugs intoxication are hyperactivity, rapid speech and dilated pupils." (UNODC 2019, p. 34) "Serotonergic syndrome is caused by an excess of serotonin in the central nervous system associated with the use of ATS. It can result in uncontrollable muscle spasms, tremor, seizures, psychosis, high blood pressure, high body temperature >400C (hyperthermia) and release of myoglobin from muscles and blood clotting in vessels (disseminated intravascular coagulation), which may lead to severe diseases and potentially death." (UNODC 2019, p. 34) • Amphetamine use was associated with an increased incidence of non-fatal overdose/poisoning in one review (Marshall & Werb 2010)[1]; Farrell 2019[2] identified this as Level C evidence (findings across cohorts of drug users). • Cocaine use was associated with an increased incidence of non-fatal overdose/poisoning in one review (Martin 2015). Farrell 2019[2] this as Level C evidence (findings across cohorts of drug users) • Suicide mortality across people with regular or problematic amphetamine use: Crude mortality per 100 patient-years 0.20 (0.07–0.55), standardized mortality ratio 12.20 (4.89–30.47) Farrell 2019[2] • Suicide mortality across people with regular or problematic cocaine use: Crude mortality per 100 patient-years 0.07 (0.04–0.10), standardized mortality ratio 6.26 (2.84–13.80) Farrell 2019[2], citing *Peacock A, University of New South Wales Sydney, personal communication. • "While fatal overdoses on stimulants do occur, these are seldom seen among PWUS who frequently use high doses. This is most likely because of the development of tolerance. Heart attacks, arrhythmia and strokes are the most frequent cause of overdose for people who use cocaine (Jean-Paul Grund et al. 2010). Overdoses of methamphetamine can lead to seizures, heart attacks, stroke, kidney failure and potentially fatal elevated body temperatures (Matsumoto et al., 2014). Combined use of cocaine with opioids, alcohol and other depressants is closely linked to cocaine overdoses, just as the use of cocaine is associated with increased chances of opioid overdoses (Jean-Paul Grund et al. 2010)" (Rigoni et al., 2018, p. 19)

	• "increase in emergency room visits related to the use of methamphetamine (rising from 68,000 in 2007 to 103,000 in 2011) in the US,[51]" (Stone 2018, p117)[3] • Rates of drug overdose deaths involving (psycho)stimulants increased 23% between 2008 and 2015. (Stone 2018, p117)[3] • "Characteristics and behaviors that were independently associated with an increased risk of a recent overdose were having had a prior overdose (odds ratio [OR], 28.58; 95% confidence interval [CI] = 14.10 to 57.96), using cocaine/crack in the past six months (OR, 2.07; 95% CI = 1.25 to 3.45), using alcohol in the past six months (OR, 1.90; 95% CI = 1.01 to 3.57), experiencing serious withdrawal symptoms in the past two months (OR, 2.70; 95% CI = 1.58 to 4.61), and younger age." (Coffin et al., 2007, p. 616) • In a qualitative study of 41 heroin/fentanyl and MA users, "Most participants believed that methamphetamine could help prevent and/or reverse an opioid-related overdose. Nearly half had personally used it to help manage overdose risks related to [non-pharmaceutical fentanyl-type drugs] NPF (Daniulaityte et al., 2022, p. 1). • "Good Samaritan laws] GSLs with protections against arrest enactment in conjunction with a [Naloxone Access Laws] NAL were associated with 7% lower rates of all overdose deaths (rate ratio (RR): 0.93% Credible Interval (CI): 0.89–0.97), 10% lower rates in opioid overdose deaths (RR: 0.90; CI: 0.85–0.95) and 11% lower rates of heroin/synthetic overdose mortality (RR: 0.89; CI: 0.82–0.96) two years after enactment, compared to rates in states without these laws. Significant reductions in overdose mortality were not seen for GSLs with protections for charge or prosecution" (Hamilton et al., 2021, p. 2)
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Overdose risk behavior	N/A	Review of reviews: Farrell 2019[2] (Not assessed)	Brief interventions reduced overdose risk behaviors in opioid users (IRR=0.72, 95% CI 0.59 to 0.87). • Bohnert AS, Bonar EE, Cunningham R, et al. A pilot randomized clinical trial of an intervention to reduce overdose risk behaviors among emergency department patients at risk for prescription opioid overdose. Drug and Alcohol Dependence 2016; 163: 40-7. Level B evidence (findings across representative, population-based cohorts) • Evidence drawn from people who might or might not have a substance use disorder	Interventions to reduce stimulant related harms

			Author conclusion: "Overdose prevention approaches to stimulants emphasise awareness of drug strength and avoiding high-dose toxicity complications, such as seizures, by reducing dose. No substantial attention has been given to reducing accidents and injuries, nor to reducing cardiovascular risk in this population."	
Correct overdose response	N/A	Systematic review: Clark 2014[4]	"There was some evidence that training is associated with an increased use of appropriate overdose strategies. In 3 studies (total n = 66) that compared reported responses to actual overdoses before training and 3 to 6 months after training, there was a consistent increase in reported use of sternal rubs, rescue breathing, remaining with the victim until help arrived, and placing the victim in the recovery position (Galea et al., 2006; Tobin et al., 2009; Wagner et al., 2010) and a decrease in use of inappropriate responses such as shouting at the victim, using ice or cold water, walking the victim, or injecting the victim with salt or other drugs (Galea et al., 2006; Tobin et al., 2009). Bennett and Holloway (2012) compared an OOPP-trained group (n = 28) with a nontrained comparison group (n = 38) and found that the OOPP-trained individuals were more likely to place the victim in the recovery position and call an ambulance but less likely to use CPR. The authors speculated that the decreased use of CPR was because of less perceived need for CPR, given the efficacy of naloxone." (p. 160)	Community opioid overdose prevention and naloxone distribution programs. All non-random studies, "fair" quality.
Alerting emergency medical services	N/A	Systematic review: Clark 2014[4]	"Five studies compared rates of EMS notification pre- and post-training: 2 reported a decrease in rates of notification (Tobin et al., 2009; Bennett et al., 2011), 2 reported an increase (Galea et al., 2006; Bennett and Holloway, 2012), and 1 reported no change (Wagner et al., 2010)." (p. 161)	Community opioid overdose prevention and naloxone distribution programs. All non-random studies, "fair" quality.
Overdose knowledge	N/A	Systematic review: Haegerich 2019[5]	"Patient education about opioid risks and overdose can increase patient knowledge and behavioral intentions (Dunn et al., 2017; McCarthy et al., 2015)" (p. 8)	Prevention strategies to address the opioid crisis
		Meta-analysis: Giglio 2015[6] (Not assessed)	Overdose education participants had higher naloxone administration, overdose recognition, and overdose response knowledge compared to untrained participants in 5 studies (1 RCT, 4 uncontrolled) (standardized mean difference = 1.35, 95% CI 0.92 to 1.77, $p<0.001$; $I^2=0\%$, $p=0.91$). • Gaston 2009 (cohort, quality 7/8); Green 2008 (cross-sectional, quality 6/8); Jones 2014 (cohort, quality 6/8); McAuley 2010 (cohort, quality 7/8); Williams 2014 (RCT, quality 8/8)	Effectiveness of bystander naloxone administration and overdose education programs. Quality appraisal adapted from Jinks [7] rated on eight items. Perfect score is 8/8.

		Systematic review: Clark 2014[4]	"Eight articles reported pre- and post-training measures of change in knowledge about opioid overdose" (p. 160). Most demonstrated significant increases in bystander knowledge of prevention, risk factors, and prevention of overdose, although some studies were hampered by ceiling effects, particularly among IDUs with prior knowledge regarding overdose.	Community opioid overdose prevention and naloxone distribution programs. All non-random studies, "fair" quality.

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Bohnert 2016[8]	RCT 6-month follow up Emergency Department	(1) Brief intervention: One 30 min motivational interview-based session with a Masters-level therapist emphasizing overdose risk reduction and brochures (2) Control: brochures on overdose prevention, appropriate responses and further resources alone	N= 204 ED patients who screened positive for non-medical prescription opioid use	**Overdose risk behavior**: Reduced frequency across nine risk behaviors in BI compared to control (41% vs 15%, IRR=0.72, 95% CI 0.59 to 0.87, $p < 0.01$). **Non-medical opioid use**: Reduced compared to control (50% vs 40%, $p < 0.01$). **Intentions for future non-medical opioid use**: NDS Overdose knowledge: NSD	

Evidence-Based Guidelines

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

United Nations Office on Drugs and Crime, World Health Organization (WHO), and Joint United Nations Programme on HIV/AIDS (UNAIDS). HIV prevention, treatment, care and support for people who use stimulant drugs; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf

Other Resources

Source	Recommendation	Comments

Stone & Shirley-Beavan 2018[3]	Drug Overdose Immunity and Good Samaritan Laws. National Conference of State Legislatures. Available from: https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Substantially favors intervention ☒ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. Education is an important component of change and relatively easy to implement; the importance of patient education is readily supported across a range of other medical conditions.

Subgroup Considerations

Patients with high readiness to change may have better outcomes.

Implementation Considerations

Requires combining with other HR activities. Requires clinician knowledge and comfort with harm reduction principles

References

1. Marshall BDL, Werb D. Health outcomes associated with methamphetamine use among young people: a systematic review. *Addiction*. 2010;105(6):991-1002. doi:10.1111/j.1360-0443.2010.02932.x
2. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
3. Stone K, Shirley-Beavan S. *The Global State of Harm Reduction 2018*. Harm Reduction International; 2018. Accessed November 3, 2022. https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf
4. Clark AK, Wilder CM, Winstanley EL. A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs. *J Addict Med*. 2014;8(3):153-163. doi:10.1097/ADM.0000000000000034
5. Haegerich TM, Jones CM, Cote PO, Robinson A, Ross L. Evidence for state, community and systems-level prevention strategies to address the opioid crisis. *Drug Alcohol Depend*. 2019;204:107563. doi:10.1016/j.drugalcdep.2019.107563
6. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol*. 2015;2(1):10. doi:10.1186/s40621-015-0041-8
7. Jinks A, Cotton A, Rylance R. Obesity interventions for people with a learning disability: an integrative literature review. *J Adv Nurs*. 2011;67(3):460-471. doi:10.1111/j.1365-2648.2010.05508.x
8. Bohnert ASB, Bonar EE, Cunningham R, et al. A pilot randomized clinical trial of an intervention to reduce overdose risk behaviors among emergency department patients at risk for prescription opioid overdose. *Drug and Alcohol Dependence*. 2016;163:40-47. doi:10.1016/j.drugalcdep.2016.03.018

Table 59. Education Sex

Recommendation:

1. For patients who engage in **risky stimulant use**, clinicians should: offer harm reduction education regarding risky sexual behaviors.
2. For patients who engage in **risky sexual behaviors**, clinicians should: advise patients to seek assessment and treatment in the event of a suspected exposure to STI.

Clinical Question Summary Table

Clinical Question	What are effective strategies for preventing risky sex-related harms in patients with StUD?
Population	People who engage in risky stimulant use
Intervention	Harm reduction education about risky sexual behaviors
Comparison	No education
Main Outcomes	Harm reduction related outcomes
Setting	Clinical settings
Background & Definitions	Notes: HIV • Among men who have sex with men, there is a significant association between amphetamine-type **stimulant** (amphetamine, methamphetamine, ecstasy, speed) use and HIV infection (35 studies, 56 comparisons) (Vu 2015)[1]. Prevalence rate ratios (PRR) for cross-sectional studies was 1.7 (1.47-1.98, k=29), odds ratios (OR) for case-control studies was 2.9 (2.04-4.12), and hazard ratios (HR) or relative risk (RR) for longitudinal studies was 3.13 (2.65-3.7). In subgroup analysis, no association between ecstasy use and HIV using PPV, but significant with high heterogeneity with OR and HR (14 studies). This paper also has the ratios for methamphetamine alone subgroup. • "Grund et al. (2010) have created an overview of the relation between (injection) stimulant use and HIV and HCV (Grund et al. 2010, 194–95). More recently, the UNODC (2017) also published a systematic literature review on the relation between stimulant use and HIV." (Rigoni 2018, p18)[2] Hepatitis • Over 15% of hepatitis C patients presenting to a US integrated mental health/medical clinic in the were using stimulants (Dieperink, E., et al. 2013). They were more likely to be followed by a co-located mental health clinician than other groups. Stimulant users were more depressed (higher BDI scores) and used alcohol to a greater degree (higher AUDIT-C scores) than nonusers but were as likely to initiate and finish antiviral therapy. • Why people who use stimulants are at risk of **Hepatitis B**: Condomless sex with a partner living with HBV increases the odds of HBV transmission, particularly in the setting of dry mucosa and tissue tearing secondary to stimulant use. (SAMHSA 2021)[3] STIs • Among young adults (18-28) in the US, non-injection **crack/cocaine use** is associated with moderate elevations in the prevalence of biologically confirmed STIs (N=14,322, adjusted prevalence ratio (APR): 1.63, 95% CI: 1.10–2.42) even after adjusting for age

	at first sex, socio-demographic factors (particularly race), and alcohol and other drug use. (Khan 2013)[4] The association did not materially change when further adjusting for indicators of multiple partnerships, inconsistent condom use, and sex with an STI-infected partner in the past year (APR: 1.69, 95% CI: 1.13–2.52), suggesting these risk indicators did not explain the moderate elevations in STI levels observed. • "Cocaine use carries a significant increased risk of sexually transmitted infections such as syphilis, trichomoniasis, hepatitis C, HIV, and human papillomavirus and associated complications such as precancerous cervical abnormalities and pelvic inflammatory disease, and invasive pneumococcal disease." SAMHSA 2021 (p58)[3] • Crack/cocaine smokers were more likely to have a history of gonorrhea (36.7% vs 43.1%) and syphilis (12.7% vs 9.7%) compared to injection drug users (who may or may not smoke crack/cocaine). They were, however, the less likely to have had hepatitis (6.5% vs 18.6%) or to be HIV positive (7.8% vs 11.7%). (Booth 2020)[5] Risky sex • "the odds of engaging in risky sex for heterosexual **methamphetamine** users is, on average, between 37% and 72% greater than for non-methamphetamine users" in a meta-analysis of 24 studies including 287,781 individuals (Hittner 2016)[6]. unprotected intercourse, OR 2.22 (95% CI: 1.80 –2.74); Unprotected anal sex, OR 2.45 (95% CI: 1.62–3.72); inconsistent condom use, OR 1.93 (95% CI: 1.57–2.37); sex with multiple partners, OR 2.99 (95% CI: 1.84 –4.84). • "The use of methamphetamine in particular has been associated with increased risky sexual behaviours, in part by increasing sex drive and enable longer sexual episodes (Hunter et al. 2012)." (Rigoni 2018, p19)[2] • Molitor F, Truax SR, Ruiz JD, et al. Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. West J Med 1998;168(2):93-7; http://www.ncbi.nlm.nih.gov/pubmed/9499742. • Stimulant drug use and risks of HIV/HBV/HCV transmission: Transmission risks through concurrent stimulant drug use and unprotected sex "Inconsistent condom use by people who use stimulant drugs has been identified as a prime means of contracting STIs, including HIV, particularly as a result of the concurrent use of stimulant drugs with frequent sexual activity of long duration with multiple partners or in groups. Stimulant drug use may also facilitate longer penetration (which can lead to condom breakages), and more intense acts such as fisting that increase the opportunity of anal and vaginal tears or bleeding." UNDOC 2019 (p15)[7] • "People who have sex while under the influence of stimulant drugs are more likely to engage in sexual risk behaviours, especially unprotected sex [83]. They may have reduced sexual inhibitions and a feeling of invincibility, which makes choosing or remembering to use a condom more challenging. Other factors that can contribute to inconsistent condom use include lack of access to condoms and lubricants when needed, poor safe-sex negotiations skills, being on PrEP [84] and engaging in risk-reduction strategies such as serosorting or strategic positioning." UNDOC 2019 (p21)[7] • "An additional risk [of infectious diseases (eg blood-borne viruses such as HCV and HIV)] for people who inject stimulants is that they… engage more frequently in risky sexual activities **compared to people who inject heroin** (Grund et al. 2010; Folch et al. 2009)" (Rigoni 2018, p18)[2] Multiple causes • "MA is also implicated in a host of infectious diseases, such as skin infections (cellulitis, skin abscesses), methicillin-resistant Staphylococcus aureus (MRSA), sexually transmitted infections, and opportunistic fungi (eg, Histoplasma capsulatum; Salamanca et al., 2015). **High-risk sexual behaviors**, **malnutrition**, **harmful effects of MA on immune system functioning**, and **inflammation** likely contribute to infectious disease risk." SAMHSA 2021 (p58)[3]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **IDU**: Injection drug use/users, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MSM**: Men who have sex with men, **N**: Number, **NSD**:

	No significant difference, **PWID**: People who inject drugs, **RCT**: Randomized Control Trial, **SMD**: Standard Mean Difference, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence [i]	Source (Quality [ii])	Effect/Impact	Comments
Critical/Important Outcomes				
STI acquisition	N/A	Meta-analysis: Henderson 2020[8] (Not assessed)	Moderate quality evidence that **behavioral counseling interventions** reduce the likelihood of acquiring STIs in sexually active adolescents and in adults at increased risk for STI (3 to 17 months' follow-up) (19 trials, n=52 072, OR=0.66 [0.54, 0.81], p<0.001; I^2=74%). Significant effect for studies with low contact time interventions (< 30 mins) (4 trials, n=39,230, OR=0.66 [0.36, 1.24]; I^2=43.6). Nearly all studies were conducted among populations at increased risk (20/21 [95%]) for STI. Increased risk populations were defined by STI clinic attendance or STI history (highest risk), inconsistent condom use, multiple sex partners, or demographic characteristics associated with high STI incidence. Most interventions were conducted in general primary care, obstetrics and gynecology, STI clinics, women's health clinics, adolescent medicine, and family planning clinics. STI incidence rates were highly variable across studies; control group rates ranged from 0% to 50%, while intervention group rates ranged from 0% to 37%. • In-person behavioral counseling (group only or group + individual): DiClemente et al, 2004* Shain et al, 2004* Jemmott et al, 2005* Jemmott et al, 2007* Kershaw et al, 2009 Neumann et al, 2011* Champion and Collins, 2012* Wingood et al, 2013* • In-person behavioral counseling (individual only): Jemmott et al 2007* Crosby et al, 2009* Marrazzo et al, 2011 Berenson and Rahman, 2012 Metsch et al, 2013 • Media-based interventions without in-person counseling: Peipert et al, 2008 Warner et al, 2008* Carey et al, 2015 Bailey et al, 2016 Free et al, 2016 Tzilos Wernette et al, 2018 Shafii et al, 2019 * Study reported statistically significant reduction in 1 or more STI acquisition outcome.	USPSTF systematic review on behavioral counseling in primary care
Risky sex behavior	N/A	Review of reviews: Tran 2021[9] (Not assessed)	**Psychosocial intervention** groups had lower odds of self-reported unsafe sex risk behaviors at the end of trial compared to control groups in 2 studies of people who use ATS (n=784, RR=0.6 [0.46, 0.79], p<0.001; moderate-quality evidence) • Radfar 2017[10] (n=357 MA use, Harm reduction psychoed vs Control) • Strona 2006[11] (n=178 MA use MSM, Positive Reinforcement Opportunity Project [PROP] vs Control)	Review of systematic reviews on psychosocial interventions for **ATStUD**

		Meta-analysis: Henderson 2020[8] (Not assessed)	**Behavioral counseling interventions** conducted in primary care settings in the US were associated with self-reported reduced STI risk behavior (3 to 14 months' follow-up) (n = 5253, OR=1.31 [95% CI 1.10, 1.56]; I^2 = 40%). There was limited evidence on persistence of effects beyond 1 year for the few studies reporting extended follow-up beyond 1 year. Most of included evidence (30/34 [88%]) was from studies of people at increased risk for STI. Increased risk populations were defined by STI clinic attendance or history (highest risk), sexual risk behaviors, or demographic characteristics. Most interventions were conducted in general primary care, obstetrics and gynecology, STI clinics, women's health clinics, adolescent medicine, and family planning clinics.	USPSTF systematic review on behavioral counseling in primary care

		Meta-analysis: Pantalone 2020[12] (Not assessed)	**Interventions co-targeting sexual risk behavior and** mental health, alcohol, and/or drug use among SMM had a small, positive, significant effect on reducing sexual risk behavior (12 studies, d=0.17 [0.02, 0.32], p=0.022). Mixed population of participants with one or more mental health, alcohol, or drug use problem.
			• Drug use & sexual risk behavior interventions:
			  ○ Landovitz 2015 (n=140 HIV- Stim, 8 wks CM vs NCR) NSD in unprotected anal sex (p=0.51)
			  ○ Parsons 2014 (n=143 HIV- Drug use [68% cocaine, 17% MA] non-tx-seeking MSM, 4-session MI for HIV & substance use vs 4-session Education control) NSD in unprotected anal intercourse (p=0.43)
			• Alcohol use & drug use & sexual risk behavior interventions:
			  ○ Kurtz 2013 (n=515 AOD [62% stim], 4-session group BI vs 1 session Control) NSD in sexual risk behavior (p=0.4)
			  ○ Mansergh 2010 (n=1686 AOD, 6-session group CBT 'Project MIX' vs Control) NSD in unprotected anal sex (p=0.25)
			  ○ Safren 2013 (n=201 HIV+ AOD, 9-sessions Case management vs Standard care) NSD in transmission risk behavior (p=0.57)
			• Alcohol use & sexual risk behavior interventions:
			  ○ Kahler 2018 (HIV+ Alcohol, 3-session MI 'Project ReACH' vs Referral) Favorable for unprotected sex (d=0.37 [0.06, 0.68], p=0.02)
			  ○ Pachankis 2015 (HIV- Alcohol, 10-session 'ESTEEM' vs Wait-list) Favorable for unprotected anal sex (d=0.59 [0.09, 1.09], p=0.022)
			  ○ Velasquez 2009 (HIV+ MSM Alcohol use disorder, 8-session TTM+MI vs Referral) Favorable for unprotected anal sex w/ alcohol use (d=0.59 [0.31, 0.86], p<0.001)
			• Mental Health & sexual risk behavior interventions:
			  ○ Brown 2019 (HIV+ Mental Health, 3-session 'Poz Talk' vs Wait-list) NSD in unprotected anal sex (p=0.2)
			  ○ O'Cleirigh 2019 (HIV- Mental Health, 10-session CPT+HIV risk counseling vs HIV counseling & testing) NSD in sexual risk behaviors (p=0.11)
			  ○ Williams 2008 (HIV+ Mental Health, 6-session group S-HIM vs SHP Control) NSD in sexual risk behavior (p=0.75)
				Behavioral interventions for **Sexual Minority Men (SMM)** co-targeting **mental health, alcohol and drug use**, as well as sexual risk behavior, antiretroviral adherence, and healthcare engagement

			○ Williams 2013 (HIV+ Mental Health, 6-session group S-HIM vs HP Control) NSD in unprotected receptive anal sex (p=0.92) Out of the 13 RCTs of interventions targeting sexual risk behavior and drug use among SMM, 5 RCTs identified between-group differences in reductions in sexual risk behavior. • Carrico, Nation 2015 (n=23 HIV+ MA use, 7-sessions RAP vs Control) NSD in transmission risk at 3 months • Carrico, Gomez 2015 (n=21 MA, 12-wks CM + 5-sessions ARTEMIS vs CM) NSD in transmission risk at 6 months • Kurtz 2013 (n=515 AOD [62% stim], 4-session group BI vs 1 session Control) NSD in sexual risk behavior (p=0.40). • Landovitz 2015 (n=140 HIV- Stim, 8 wks CM vs NCR) NSD in unprotected anal sex (p=0.51) • Mansergh 2010 (n=1686 AOD, 6-session group CBT 'Project MIX' vs Control) NSD in unprotected anal sex (p=0.25) • Morgenstern 2009 (n=150 MSM Club drugs [60% StUD], 4-session MI vs Control) NSD in number of unprotected sex acts. Favorable for number of casual sex partners (d=0.64). • Parsons 2014 (n=143 HIV- Drug use [68% cocaine, 17% MA] non-tx-seeking MSM, 4-session MI for HIV & SU vs 4-session Education control) NSD in UAI (p=0.43) • Parsons 2018 (n=210 HIV+ MA, 8 session MI+CBT vs control) NSD in unprotected anal sex • Rotheram-Borus 2004 (n=175 HIV+ Drug, 18-session In-person BI vs Telephone BI vs Wait-list) In-person BI significantly reduced number of unprotected sex acts compared to waitlist (p<0.01), but telephone BI did not. • Safren 2013 (n=201 HIV+ AOD, 9-session Case management vs Standard care) Intervention had a greater effect on reducing transmission risk behavior among depressed patients (OR=0.11 [0.02-0.45], p<0.01), but NSD between groups in non-depressed patients (OR=1 [0.81-1.25]). • Santos 2014 (n=236 HIV- AOD, 1-session Personalized cognitive counseling vs Standard care) Favorable for unprotected anal intercourse w/ MA use (RR=0.26 [0.08-0.84], p=0.02) • Shoptaw 2005 (n=162 MaUD, 48-session CBT vs CM vs CBT+CM vs GCBT) GCBT had greater reduction in unprotected receptive anal intercourse compared to other groups at 1 month (p< 0.01), but NSD at later follow-ups. • Shoptaw 2008 (n=128 AUD/StUD, 48-session GCBT vs GSST) NSD between groups Uncontrolled studies of interventions targeting drug use and sexual risk behavior among SMM • Carrico 2014 (Study 2) (n=88 MA, The Stonewall Project) • Esposito-Smythers 2014 (n=17 HIV+ Alcohol/cannabis use disorder, 15-session CBT+CM) • Landovitz 2012 (n=53 HIV- MA, 8 wks CM) • Mimiaga 2012 (n=16 HIV- Stim use, 10-session BA-RR) • Reback 2017 (n=585 Drug use, 'GUYS')	

			• Smith 2017 (n=33 HIV- Alcohol/drug/mental health, 8-session Project PRIDE) • Wu 2011 (n=68 MA, 7-session Connect with Pride) • Zule 2012 (n=31 MA, 1-session MI 'MASH')	
		Systematic review: Elkbuli 2019[13]	HIV prevention interventions targeting adult HIV-negative **injection drug users**: Reduction in frequency of risky sexual behaviors were observed in 33% of studies targeting PWID (n=9) • Copenhaver 2007 [16] (pre-post n=226 in MMT [73% PWID]) Favored intervention in IDU risk and sex risk • Vera 2012 [18] (RCT n=584 female sex workers IDU) NSD between group in IDU risk or sex risk • Booth 1998 [14] (RCT n=3743 out-of-tx PWID) Decreased IDU risk, but NSD between groups • Booth 2011 [15] (RC, n=623 in tx PWID) Decreased IDU risk, but NSD between groups • Tobin 2011 [17] (RCT n=227 PWID) Favored intervention in IDU risk and sex risk • Mihailovic 2015 [19] (RCT n=227 PWID) Favored intervention in IDU risk and sex risk • Goswami 2014 [20] (pre-post n=3349 PWID) Favored intervention in IDU risk and sex risk • Simmons 2015 [21] (RCT n=1123 male PWID) Favored intervention in IDU risk • Des Jarlais 2014 [23] (longitudinal n=7132 PWID) Mixed: NSD in sex risk among HIV seronegative participants, decreased unprotected sex among HIV seropositive participants HIV prevention interventions targeting adult HIV-negative **non-injection drug users**: (n=10) Reduction in frequency of risky sexual behaviors were observed in 64% of studies targeting non-IDUs (n=10) • Nydegger 2013 [28] (n=143) • Tross 2008 [30] (n=384 female) • Calsyn 2013 [23] (n=66) • Kurtz 2013 [31] (RCT n=515 MSM AOD [62% Stimulant use]) NSD in sexual risk behavior • Mansergh 2010 [24] (RCT n=1686 MSM AOD) • McMahon 2001 [25] (n=149 male) • McMahon 2013 [26] (n=660) NSD • Mimiaga 2012 [27] (n=16 MSM Stimulant use) • Herrmann 2013 [29] (RCT n=56 CoCUD) Favors intervention • Surratt 2014 [32] (n=597 female)	HIV prevention interventions targeting adult HIV-negative **substance users**
		Systematic review: Knight 2019[14]	Among the 23 studies of gay, bisexual or other men who have sex with men with a diagnosis of ATS dependence that included measures of sexual health-related outcomes, 18 reported a statistically significant effect on one or more sexual health-related outcomes such as having sex while under the influence of drugs or engaging in condomless anal intercourse (CAI). **Motivational Interviewing:** 2/2 studies reported positive effect on sexual health-related outcomes • Favors MI: Parsons 2014 (RCT); Zule 2012 (Pre-post) **Contingency management**: 5/8 studies reported positive effect on sexual health-related outcomes	Interventions to address substance use and sexual risk among **MA-using MSM**

			• Favors CM: Reback and Shoptaw, 2014 (RCT); Landovitz et al., 2012 (Pre-post, MaUD); Shoptaw et al., 2005 (RCT, n=162 MaUD); Shoptaw et al., 2008 (RCT); Strona et al., 2006 (Pre-post, MaUD) • NSD between groups in effect: Menza et al., 2010 (RCT); Nyamathi et al., 2017 (RCT); • No effect: Carrico 2015a (RCT) **Other Psychosocial intervention**: 6/7 studies reported positive effect on sexual health-related outcomes • Favors other psychosocial: Lyons et al., 2014 (Pre-post); Mimiaga et al., 2012 (Pre-post); Reback et al., 2012 (Pre-post); Reback and Fletcher, 2017 (Pre-post); Santos 2014 (RCT); Wu et al., 2011 (Pre-post) • NSD between groups: Shoptaw et al., 2008 (RCT); **Harm reduction**: 1/1 studies reported positive effect on sexual health-related outcomes • Carrico et al., 2014 (Pre-post, 211 MA-using MSM, The Stonewall Project) **Pharmacotherapy**: 2/4 studies reported positive effect on sexual health-related outcomes • Colfax et al., 2011 (RCT, MaUD, Mirtazapine) decreases in sexual risk behavior, including the number of partners and episodes of CRAI and CIAI • Santos et al., 2016 (RCT Naltrexone) sexual risk reductions, including reductions in sero-discordant receptive anal intercourse and sero-discordant CRAI • NSD between groups in effect: Coffin 2018 (RCT, MaUD, Extended-release naltrexone); Das et al. 2010 (RCT, MaUD, Bupropion)	
		Meta-analysis: Meader 2013[16]	1) Multi-session psychosocial interventions vs Standard education among people who misuse drugs **Multisession psychosocial interventions** had greater reduction in HIV sex risk behaviors compared to educational interventions (k=46, 16504 participants, OR=0.86, [0.77, 0.96], p=0.007; I^2=53%, p<0.001). • Studies that recruited participants receiving substance misuse treatment appeared to show greater effectiveness than studies of participants who were not in substance misuse treatment. • No evidence that publication date, location (US vs non-US), receiving HIV testing, type of drug use, or inclusion of condom skills training impacted effectiveness. Also favored when analysis restricted to: • RCTs only and worst-case scenario for missing data (k=26, OR=0.81, [0.68, 0.97]; I^2=64%). GRADE rating: Moderate • PWID only (k=30, OR = 0.84 (0.73, 0.95); I^2=49). GRADE rating: Moderate **No significant difference** when analysis restricted to PWID and/or **crack use** (k=12, OR = 0.86 (0.67, 1.12); I^2=66). GRADE rating: Low (2) Multi-session psychosocial interventions vs Minimal control among people who misuse drugs **Multi-session psychosocial interventions** greater reduction of HIV sex risk behaviors compared to minimal interventions (k=7, 3028 participants, OR=0.60, [0.46, 0.78], p<0.001; I^2=53%, p=0.05).	HIV sex risk behaviors of adults who use **drugs** Johnson 2020 [17]'s rating: PRISMA 26/27, AMSTAR 11/11

			GRADE rating: Low. Including RCTs only (k=6, OR=0.58, [0.41, 0.80]; I^2=55%). GRADE rating: Moderate • Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) • Baxter 1991 (n=134 PWID in prison, 6-session Psychoeducation vs Control) • CDC 1999 (n=2218) • Schilling 1991 (n=91 women in MMT [cocaine 42%], 5-session Psychoeducation vs Standard education) • Sorensen 1994a (n=60 in opiate detox, 2-session Psychoeducation vs Control) • Sorensen 1994b (n=50 in MMT, 3-session Psychoeducation vs Control) • Wechsberg 2004 (n=420 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist	
		Meta-analysis: Meader 2010 [18] (Not assessed)	35 RCTs on multi-session psychosocial interventions designed to reduce injection and/or sexual risk behavior in comparison with standard education and minimal intervention controls for people who misused opiates, cocaine, or a combination of these drugs. *(1) Multi-session psychosocial interventions vs Standard education* **No significant difference** in sexual risk behaviors at 3-6-month follow-up in 6 RCTs (n= 1050, p=0.24), heterogeneity (I^2=49%, p=0.08). • Avants 2004 (n=220 PWID in MMT [46% CoUD], 12-session Psychoeducation vs 1-session MI + Standard care [2 hours counselling and case management per month]) • Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) • Dushay 2001 (n=539 Puerto Rican or Black, 3-session culturally-appropriate Psychoeducation vs 2-session Standard education) • Eldridge 1997 (n=104 court-mandated IPT, 6-session Psychoeducation vs 2-session Standard education) • Harris 1998 (n=204 women in MMT, 16-session women-focused Psychoeducation vs Standard care [MMT]) • O'Neill 1996 (n=92 PWID in MMT, 6-session Psychoeducation vs Standard care) **No significant difference** in sexual risk behaviors at >6-month follow-up in 2 RCTs (n=203, p=0.86) • Harris 1998 (n=204 women in MMT, 16-session women-focused Psychoeducation vs Standard care [MMT]) • O'Neill 1996 (n=92 PWID in MMT, 6-session Psychoeducation vs Standard care) **No significant difference** in the proportion of participants engaging in safer sexual behavior at 3-6-month follow-up in 8 RCTs (k=14, n= 3731, p=0.19), heterogeneity (I^2=39%, p=0.07). • El-Bassel 1995 (n=145 incarcerated women, 16-session psychoeducation vs 2-session Standard education) • Eldridge 1997 (n=104 court-mandated IPT, 6-session Psychoeducation vs 2-session Standard education)	Cochrane Review of psychosocial interventions for reducing injection and sexual risk behavior for preventing HIV in **drug users** (opioids/cocaine) Johnson 2020 [17]'s rating: PRISMA 23/27, AMSTAR 10/11

			• Kotranski 1998 (n=417 PWID, 3-session Psychoeducation vs 2-session Standard education) • Malow 1994 (n=152 Crack CoUD, 3-session Psychoeducation vs Standard education) • Margolin 2003 (n=90 MMT, 6-session Psychoeducation vs Group counseling) • NADR (k=7, Psychoeducation vs Standard education) • Sterk 2003 (n=68 Black women WID, 4-session Motivational HIV Psychoeducation vs 4-session Behavioral HIV Psychoeducation vs NIDA Standard HIV Intervention) • Wechsberg 2004 (n=60 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist) **No significant difference** between Multi-session psychosocial interventions and Minimal control in the proportion of participants engaging in safer sexual behavior at >6-month follow-up in 1 RCT (n=412, p=0.29) • Wechsberg 2004 (n=60 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist) *(2) Multi-session psychosocial interventions vs Minimal control* **Multi-session psychosocial interventions** had greater reductions in sexual risk behaviors compared to Minimal control in 4 RCTs (n=253, SMD= -0.31 [-0.56, -0.06], p=0.01). • Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) • Schilling 1991 (n=91 women in MMT, 5-session Psychoeducation vs Standard education) • Sorensen 1994a (n=60 in opiate detox, 2-session Psychoeducation vs Control) • Sorensen 1994b (n=50 in MMT, 3-session Psychoeducation vs Control) **Multi-session psychosocial interventions** had more participants engaging in safer sexual behavior compared to Minimal control in 1 RCT (n=420, RR= 1.34 [1.03, 1.73], p=0.03). • Wechsberg 2004 (n=60 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist) NSD *(3) Standard education vs Minimal control* **No significant difference** between Standard education and Minimal control in sexual risk behaviors at 3-6-month follow-up in 3 RCTs (n= 263, p=0.42) • Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) • Baker 1994 (n=200 out-of-tx PWID, 1-session MI vs Standard care) • Tucker 2004 (n=145 PWID, 1-session MI vs Booklet) **No significant difference** between Standard education and Minimal control in the proportion of participants engaging in safer sexual behavior at 3-6-month follow-up in 2 RCTs (n= 296, p=0.75) • Gibson 1999a (n=220 completing OUD detox, 1-session Standard education vs Booklet) • Gibson 1999b (n=76 completing OUD detox, 1-session Standard education vs Short interview)	

		Meta-analysis: Colfax 2010[19] (Not assessed)	**No significant difference** between behavioral interventions vs passive or minimal treatment in reduction of sexual risk behaviors in stimulant users (2 RCTs, 390 participants, SMD= −0.12, [−0.33, 0.09]) • Mausback 2007a (n=182 MA use, 'Fast Lane' 4-session sex-risk intervention vs Control) • Mausback 2007b (n=208 MA use HIV+ MSM, 'EDGE' 5-session sex-risk intervention vs Control) **No significant difference** between high-intensity or adjunctive behavioral interventions vs active SUD treatment in reduction of sexual risk in stimulant users (3 RCTs, k=4, 1063 participants, SMD=0.04, [−0.18, 0.26]). • Shoptaw 2005 (n=162 MaUD MSM, GCBT vs CBT vs CM vs CM+CBT) • Shoptaw 2008 (n=72 ATStUD MSM, GCBT vs GSST) • Sherman 2009 (n=864 MA use, Peer education vs Life skills)	**ATS** and HIV Johnson 2020[17]'s rating: PRISMA 22/27, AMSTAR 10/11
Unprotected sex	N/A	Systematic review: Carrico 2016[20]	**Behavioral interventions** reduced condomless anal intercourse in 2 out of 5 RCTs targeted MA-using MSM • Shoptaw 2005 (n=162 MA-using MSM, CBT vs CM vs CM+CBT vs G-CBT) Favored G-CBT • Carrico 2015a (n=23 MA-using HIV+ MSM, Expressive writing vs Control) NSD • Carrico 2015b (n=21 MA-using MSM, ARTEMIS+CM vs CM) NSD • Mausbach 2007 (n=341 MA-using HIV+ MSM, 'EDGE' 5-session safer sex CBT vs Control) Favored EDGE • Menza 2010 (n=127 MA-using MSM, CM vs Control) NSD	Behavioral interventions for **substance-using MSM**
		Meta-analysis: Johnson 2008[21] (Not assessed)	**Behavioral intervention vs Minimal to no HIV prevention** • **Behavioral interventions** reduced the number of episodes of or partners for unprotected sex by 27% (40 studies, 11864 participants, RR= 0.73 [0.63, 0.85], p<0.001). This represents a decrease from an average of 10.1 unprotected occasions to 7.4 in a 6-month period, and from 1.2 partners for anal sex without condoms to 0.9 in a 6-month period). The effect was significant for small group and community-level interventions, but not for individual-level interventions. • **Behavioral intervention** reduced the proportion reporting unprotected sex by 23% (40 studies, PR= 0.77 [0.72, 0.83], p<0.001). This represents a decrease from an average of 41% reporting unprotected sex to 32%. The effect was significant for small group, individual-level, and community-level interventions. **Experimental intervention vs Standard or Other HIV prevention** • **Experimental Interventions** reduced the number of episodes of or partners for unprotected sex by 17% beyond changes observed in standard or other HIV prevention interventions (18 studies, 6721 participants, RR=0.83 [0.73, 0.95], p=0.01). The effect was significant for individual-level interventions and trended for small group interventions (p=0.06). • **Experimental Interventions** reduced the proportion reporting unprotected sex by 7% beyond changes observed in standard or other HIV prevention interventions (18 studies,	Cochrane Review of behavioral interventions to reduce risk for sexual transmission of HIV among **MSM**

			6721 participants, PR=0.93 [0.89, 0.97], p<0.001). The effect was significant for individual-level interventions and small group interventions. "Summary effects of interventions including each type of content were statistically significant except for those including technical skills and those including "other" content. The most favorable effect by intervention content, a 38% reduction in risky behavior, was observed among interventions addressing perception of risk and losses ("unsafe sex puts you at risk") rather than gains ("safer sex protects you")." (p. 9)	
Injection and sexual risk behavior combined	N/A	Meta-analysis: Meader 2010[18] (Not assessed)	35 RCTs on multi-session psychosocial interventions designed to reduce injection and/or sexual risk behavior in comparison with standard education and minimal intervention controls for people who misused opiates, cocaine, or a combination of these drugs. *(1) Multi-session psychosocial interventions vs Standard education* **Trend towards Multi-session Psychosocial Interventions** having greater reductions in sexual and injection risk behaviors compared to Standard education in 11 studies (n=1427, SMD= -0.17 [-0.37, 0.03], p=0.09) with significant heterogeneity ([I^2=62%, p<0.001). **Significant effect** for participants in formal drug treatment (8 studies, n=706, SMD=-0.28 [-0.44, -0.12], p<0.001; [I^2=10%, p=0.36]). • Avants 2004 (n=220 PWID in MMT [46% CoUD], 12-session Psychoeducation vs 1-session MI + Standard care [2 hours counselling and case management per month]) • Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) • Eldridge 1997 (n=104 court-mandated IPT, 6-session Psychoeducation vs 2-session Standard education) • Harris 1998 (n=204 women in MMT, 16-session women-focused Psychoeducation vs Standard care [MMT]) • O'Neill 1996 (n=92 PWID in MMT, 6-session Psychoeducation vs Standard care) • Schilling 1991 (n=91 women in MMT, 5-session Psychoeducation vs Standard education) • Sorensen 1994a (n=60 in opiate detox, 2-session Psychoeducation vs Control) • Sorensen 1994b (n=50 in MMT, 3-session Psychoeducation vs Control) **No effect** for participants not in formal treatment (3 studies, n=721, SMD=0.11 [-0.32, 0.54], p=0.61) with significant heterogeneity (I^2=76%, p=0.02). • Baxter 1991 (n=134 PWID in prison, 6-session Psychoeducation vs Control) • Dushay 2001 (n=539 Puerto Rican or Black, 3-session culturally-appropriate Psychoeducation vs 2-session Standard education) • Sterk 2003 (n=68 Black women WID, 4-session Motivational Psychoeducation vs 4-session Behavioral Psychoeducation vs Standard education) **Multi-session Psychosocial Interventions** had more participants engaging in safer injection and sexual risk behavior compared **to Standard Education** in 11 studies (k=17, n= 5763, RR= 1.12 [1.04, 1.2], p<0.001). Significant heterogeneity (I^2=64%, p=0.01).	Cochrane Review of psychosocial interventions for reducing injection and sexual risk behavior for preventing HIV in **drug users (opioids/cocaine)** Johnson 2020[17]'s rating: PRISMA 23/27, AMSTAR 10/11

			Significant effect for participants in formal drug treatment (3 studies, 341 participants, RR= 1.42 [1.14, 1.77], p<0.001; [I2=0%, p=0.45])) • Eldridge 1997 (n=104 justice-involved tx, 6-session Psychoeducation vs 2-session Standard education) • Malow 1994 (n=152 Crack CoUD, 3-session Psychoeducation vs Control) • Margolin 2003 (n=90 MMT, 6-session Psychoeducation vs Group counseling) **Significant effect** for participants not in formal drug treatment (7 studies, k=13, 5277 participants, RR= 1.10 [1.02, 1.18], p=0.01; [I2=67%, p<0.001]). • Colon 1993 (n=1866, 3-session Psychoeducation vs Control) • Deren 1995 (n=1770 PWID or partner, 3-session Psychoeducation vs 1-session Standard education) • El-Bassel 1995 (n=145 incarcerated women, 16-session psychoeducation vs 2-session Standard education) • Kotranski 1998 (n=417 PWID, 3-session Psychoeducation vs 2-session Standard education) • NADR (k=7) • Robles 2004 (n=557 PWID, 6-session Psychoeducation vs 2-session Standard education) • Siegal 1995 (n=381 needle exchange, 4-session Psychoeducation vs 1-session Enhanced standard care) • Wechsberg 2004 (n=60 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist)	
Harms	N/A	Meta-analysis: Henderson 2020[8] (Not assessed)	No harms were identified in the 7 studies (n = 3458) reporting adverse events or possible harms related to unintended pregnancy risk or mental health.	USPSTF systematic review on behavioral counseling in primary care

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

ARTEMIS = Affect Regulation Treatment to Enhance Methamphetamine Intervention Success

BA-RR = Behavioral Activation therapy and Risk Reduction counseling

CPT = Cognitive Processing Therapy

ESTEEM = Effective Skills to Empower Effective Men

GCBT = Gay-specific Cognitive Behavioral Therapy

GSST = Gay-specific Social Support Therapy

GUYS = Guys Understanding Your Situation

HP = Health Promotion
MASH = Men's Attitudes on Sex and Health
Project PRIDE = Promoting Resilience In Discriminatory Environments
Project ReACH = Reducing Alcohol-related Comorbidities in HIV treatment,
RAP = Resilient Affective Processing
SHP = Sexual Health Promotion
S-HIM = Sexual Health Intervention for Men
TTM = Transtheoretical Model

Characteristics of Individual Studies Table

Interventions for counselors

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Hatch-Maillette 2019[22]	2x2 factorial repeated measures 3-month follow-up USA	(1) **Basic training**: 2-hour sexual risk conversation training (2) **Enhanced training**: 10 hours plus ongoing coaching.	N=60 counselors providing individual therapy at two opioid treatment programs (OTP) and two psychosocial outpatient programs	"Counselors receiving Enhanced training (n =28) showed significant improvements compared to their Basic training counterparts (n = 32) in self-efficacy, use of reflections, and use of decision-making and communication strategies with standardized patients. These improvements were maintained from post-training to 3-month follow-up."	

Interventions for stimulant users

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Carrico 2014[23]	Pre-post 1-year program Trial 1: 12-month assessment Trial 2: 6-month assessment USA Community/ Outpatient	**The Stonewall Project**: Integrated harm reduction and treatment model. Includes HR interventions (safe use, safe injection, sexual risk-reduction education) and weekly individual and twice weekly group Matrix Model-based outpatient treatment sessions.	N=211 **MA-using** MSM *Trial 1:* N=123 (66% white, 64% HIV+, 44% on ART) *Trial 2:* N=88 (67% white, 66% HIV+, 86% on ART)	*Trial 1: n*=112 (91%) completed at least one follow-up assessment **Cocaine/crack use** (ASI): Significant reductions in past 30 days of use at 12 months (incidence rate ratio [IRR]=0.54 [0.32, 0.91], p<0.005, *d*= -0.12, Δ expected= -46.3%) **MA use** (ASI): NSD **Undetectable HIV viral load**: More HIV-positive participants reported an undetectable viral load over the 12-month follow-up (OR=2.23 [1.12, 4.41], p<0.005, Cohen's *h*=0.38)	In Pantalone 2020[12], Knight 2019[14] Also see EtDT Prev Edu IDU

		strategies for patients to: (1) transition to less potent modes of MA administration (eg, injecting to smoking, smoking to snorting); (2) promoting self-care strategies while using MA; and (3) delivering education about safer injection practices with linkage to needle exchanges and access to sterile syringes.		*Trial 2: n*=85 (96%) completed at least one follow-up assessment **Cocaine/crack use** (self-report): NSD **MA use** (self-report): Significant reductions in past 30-day use at 6 months (IRR=0.71 [0.52, 0.96], p<0.05, *d*= -0.24, Δ expected= -29.4%) **Sexual risk behavior (self-report):** NSD in any UAI at 6 months. Reduction in number of anal sex partners while using MA (IRR=0.45 [0.27, 0.73], p<0.01, *d*= -0.33, Δ expected= -55.1%). Reduction in unprotected receptive anal sex on MA (OR=0.53 [0.30, 0.94], p<0.001, Cohen's *h*= -0.24) **Undetectable HIV viral load**: NSD	
Carrico, Nation et al, 2015[24]	Pilot RCT 1 month 3-month follow-up USA Outpatient	**(1) RAP**: 7 individual sessions of Resilient Affective Processing (RAP) targeting HIV-related trauma and stimulant use **(2) Control**: 7 sessions of attention matched control	N= 23 **MA-using** MSM with HIV (12 white). Self-identify as male; report having anal sex with a man in the past year; diagnosed with HIV for at least 3 months; and report using meth in the past 30 days	**MA use**: RAP reduced use at 4 weeks, but NSD at follow-up **MA craving** (VAS): NDS **Number of risky partners:** NSD **Number of partners using MA**: Decrease in RAP group (B = −1.67, p < .05), but not Control, at 3-month follow-up. **HIV-related traumatic stress** (Impact of Event Scale – Revised [IES-R]): NSD at 3 months **Treatment acceptability:** RAP participants reported greater likelihood of recommending expressive writing exercises to a friend living with HIV (*d*=0.99, p < 0.05)	In Pantalone 2020[12], who labeled this an intervention targeting drug use and sexual risk behavior
Carrico, Gomez, et al, 2015[25]	Pilot RCT 12 weeks 6-month follow-up USA Community	**(1) CM+ARTEMIS**: 12 weeks of CM + 5 individual sessions of Affect Regulation Treatment to Enhance Methamphetamine Intervention Success (ARTEMIS)	N= 21 **MA-using** MSM (48% HIV+, 48% White)	**Retention:** NSD, 18 (86%) overall **MA use** (UDT+): NSD at 6 months **MA use** (self-report): NSD in past 30-day use at 6 months **Total number of risky anal sex partners:** NSD at 6 months **Number of risky anal sex partners on MA:** NSD at 6 months	In Pantalone 2020[12], who labeled this an intervention targeting drug use and sexual risk behavior

		(2) CM: 12 weeks of CM (standard program)			Also see CM
Herrmann 2013[26]	Cross over RCT Outpatients	**(1) Brief HIV/AIDS education** **(2) Control**	N=90 cocaine-dependent outpatients	**HIV/AIDS knowledge**: Increased in BI compared to control	In Elkbuli 2019[13]
Kurtz 2013[27]	RCT 12-month follow-up USA Community	**(1) BI**: 4 session group psychological empowerment intervention including the interaction of drugs and sex among MSM + 1 session of individual goal achievement counseling **(2) Control**: 1 session (30–45 min) individual substance use risk assessment and risk reduction counseling using the RESPECT model	N= 515 non-monogamous MSM age 18-55 with **binge drinking or drug use** (63% stimulants) in the 30 days, multiple anal sex partners, and UAI in past 90 days. Recruited via participant referral, internet and print media	Follow-up 81.6 % completed all four assessments **Number of anal sex partners**: NSD between groups in reduction. Both groups reduced over time. **Unprotected anal intercourse (UAI)**: NSD in reduced frequency (p=0.402). Both groups reduced over time. **HIV transmission risk (UAI excluding when both partners are HIV+)**: NSD between groups in reduced frequency. Both groups reduced over time. **Substance use during sex**: NSD in reduced frequency (p=0.18). Both groups reduced over time. **Drug dependence symptoms**: NSD in reduced symptoms (p=0.64). Both groups reduced over time.	In Pantalone 2020[12] Also see EtDT LGBT
Landovitz 2015[28]	RCT, open-label 8 wks, 6-month follow-up USA Community	**(1) CM**: 8 weeks of individual voucher-based contingency management with reset contingent on 3/week stimulant-negative UDS **(2) NCR**: Noncontingent reward yoked to CM participant (incentives not tied to abstinence) All participants provided 4-day supply of postexposure prophylaxis (PEP) with tenofovir/emtricitabine	N= 140 MSM without HIV who used **stimulants** (MA, amphetamine, cocaine) in past 30 days, with an HIV+ or serostatus-unknown partner in prior 3 months recruited via community advertising (37.1% White)	**Stimulant use**: Greater reduction in CM group (d=0.36 [0.03, 0.70], p=0.034) **Stimulant abstinence** (UDT-): Higher rate in CM group at 6 months in bivariate analysis (M=8.9 vs 6.1, p=0.035) and after adjusting for sociodemographics (adjusted rate ratio=1.6 [1.1-2.2], p=0.01) **Unprotected anal intercourse**: Significant decrease in incidence at 6 months in CM group (MD=3.0, p<0.001), but not NCR group (MD=1.8). However, NSD between groups in incidence rate at 6 months in bivariate analysis (M=0.8 vs 1.4, p=0.43) or in adjusted rate (p=0.39). **No. of male sexual partners**: NSD between groups at 6 months in bivariate	In Pantalone 2020[12] Also see EtDT LGBT

		and education to take in the event of exposure to HIV and present for further treatment. 46 (33%) participants initiated PEP during study or follow-up period.		analysis (M=1.68 vs 1.48, p=0.60) or in in adjusted rate between groups (p=0.71). **PEP course completion**: Greater in the CM group at 6 months in bivariate analysis (71% vs 31%, p=0.03) and adjusted odds (adjusted odds ratio [AOR]=7.2 [1.1–47.9], p=0.04). **PEP medication adherence**: Higher adherence in CM group at 6 months in bivariate analysis (M=0.75 vs 0.45, p=0.05) and trend towards greater adherence in CM group in adjusted odds (AOR=4.3 [0.9–21.9], p=0.08)	
Mansergh 2010[29]	RCT 12-month follow-up	**(1) CBT**: 6 group sessions of CBT (Project MIX) **(2) Control**: 6 sessions of attention control (MSM-related content unrelated to intervention)	N= 1,686 MSM (46% HIV+, 401% white)	**Sexual risk behavior**: NSD in unprotected anal sex (d= −.07 [−.19, .05], p=0.25) **Drug use w/ unprotected anal sex**: Trend (d= −0.11 [−0.22, 0.01], p=0.085) **Alcohol use w/ unprotected anal sex**: NSD (d= -0.03, p=0.599)	In Pantalone 2020[12] Also see EtDT LGBT
Mausbach 2007a[30]	RCT 4 wks USA	**(1) BI:** 4-session safer sex behavioral intervention (‘Fast-Lane’) **(2) BI + Booster:** Fast-Lane with boosters **(3) Control**: time-equivalent diet-and-exercise attention-control	N=451 HIV-negative, heterosexual **MA users** (at least twice in the past 2 months and once in the past 30 days))	Retention 57·6% at 6 months **High-risk sexual behavior**: reduced in the context of ongoing MA use MA use	In Colfax 2010[19]
Mausbach 2007b[31]	RCT 5 weeks USA	**(1) BI**: 5-session safer sex intervention (‘EDGE’) for increasing safer sex behaviors in HIV-positive, MA-using MSM. 5 weekly and 3 monthly individual sessions	N=341 HIV-positive, **MA-using** MSM (at least twice in the past 2 months and once in the past 30 days)	Retention 61% at 4 months **Protected sex:** Higher in EDGE participants at follow-up MA use	In Colfax 2010[19]

		(2) Control: time-equivalent diet-and-exercise attention-control			
Menza 2010[32]	RCT 12 weeks, 24-week follow-up USA Community	**(1) CM alone:** Voucher-based rewards contingent on stimulant-negative UDT 2/week with escalating value **(2) Control:** Referral to community resources	N=127 non-treatment seeking **MA-using** MSM recruited via community advertising, STD or HIV clinic referral, or peer referral (55% HIV+, 54% prior 6 wk IDU of MA). Did not exclude participants who were receiving other substance use interventions. NSD in groups' reported use of outside treatment and support services.	Retention at 24 weeks was 84% **MA use (UDT+)**: No difference in percent of MA+ samples collected during intervention (adjusted* RR =1.09 [0.71, 1.56]) or follow-up (aRR=1.21 [0.95, 1.54] p = 0.11) **Sexual risk-taking behavior**: No difference during intervention in percent reporting unprotected anal intercourse (UAI) with a partner of unknown or discordant HIV status (non-concordant UAI) during intervention (adjusted** RR=0.80 [0.47–1.35]) or follow-up (aRR= 0.51 [0.21, 1.25]	Higher MA+ UDT at baseline in CM arm. *Adjusted for baseline UDT and stage of change **Adjusted for HIV status, baseline prior 6-week non-concordant UAI and other substance use. Also see EtDT Behavioral CM
Parsons 2018[33]	RCT 12-month follow-up USA Community	**(1) MI + CBT**: 8 sessions (1 hour each) of individual MI + CBT targeting MA use and HIV medication adherence ('ACE') **(2) Education**: 8 sessions (1 hour each) of education on HIV and club drug use	N= 210 adult MSM (33% white) with HIV who use **MA** (at least 1 day of use during the previous 90 days and 1 day in the last 30 days) currently taking highly-active antiretroviral therapy (HAART) with poor adherence (report missing at least 3 days of medication in the last 30 days) recruited via community advertising. Baseline information-motivation-behavioral self-efficacy (IMB, Starks et al 2017 PubMed: 28092450) profile: adherence & MA	**Follow-up:** NSD bw groups. Overall rate 82% at 12 months **MA use** (self-report): NSD bw groups in prior 30 day use (p=0.60). Both groups reduced use over time. **Medication adherence:** NSD bw groups in prior 14 day adherence. Both groups increased adherence over time. Among those with greater barriers to change ('Global Barriers' group), MI+CBT had greater improvements in adherence compared to control ($p<0.05$). **Viral load:** NSD between groups (n=186) **CD4 count:** NSD between groups (n=186)	In Pantalone 2020[12] Also see EtDT LGBT

			'Change Ready', 'Adherence Ready/ MA Ambivalent', 'Global Barriers' to changing adherence & MA	**Condomless anal sex** (self-report): NSD bw groups or IMB classification in prior 30 day use at 12 months (n=187). Both groups increased use over time.	
Safren 2013[34]	RCT 12-month follow-up USA Community	**(1) Case management**: 9 individual sessions provided by a medical social worker including counseling about living with HIV and HIV TRB risk reduction, including party drug use **(2) TAU**: Standard care	N= 201 adult MSM with HIV (74.6% white) who received HIV care in a community health center and who reported HIV sexual transmission-risk behavior (TRB) in the prior 6 months. **Alcohol or drug use not an inclusion criterion.**	Follow-up rate at 12 months 86% (n=172). **HIV transmission risk behavior:** NSD bn groups in anal intercourse acts with HIV-uninfected partners or partners of unknown status within the past three months. Reduced overall over time. Among participants with baseline depression screen (n=26), greater reduction for case management compared to TAU (RR=0.22 [0.08–0.58]). NSD among participants with negative depression screen (n=170). **Drug-use impairment** (PHQ): NSD bn groups in past 3-month impairment over time in ITT (p=0.39) **Serious adverse events**: no study-related SAEs occurred	In Pantalone 2020[12] Also see EtDT LGBT
Sherman 2009[35]	RCT 12 months Thailand	**(1)** Peer-education network intervention 7 sessions targeted stimulant use (primary) and sexual risk (secondary) **(2)** Life-skills curriculum	N=983 young MA users (at least three times in the past 3 months) (74% male)	Retention 90% at 3 months **MA use:** Reduced in peer group **Condom use**: Increased in peer group **STI incidence**: Reduced in peer group	In Colfax 2010[19] Also see EtDT Prev Peer Navigation
Zule 2012[36]	Pre-post 2-month follow-up	**MI**: Single individual session of MI (MASH)	N= 31 out-of-treatment MSM who use MA (48% HIV+, 45% White	**MA use:** Decreased **Sexual risk behavior:** Decrease in condomless anal intercourse	In Pantalone 2020[12], Knight 2019[14]
Stimulant use-focused interventions					

Reback & Shoptaw 2014[37] McDonell 2013[38]		In-treatment contingency management studies			
McKay 2013[39] Wimberly 2017[40]	RCT 24-month follow-up USA Outpatient	**(1) TAU**: Standard intensive outpatient treatment (9 hours/week of group) for 3 to 4 months then standard outpatient (1 group/week) up to 6 months total. **(2) TMC + TAU**: Telephone monitoring and adaptive counseling weekly for 8 weeks, biweekly for 44 weeks, monthly for 6 months, bimonthly for 6 months. Approximately 20 minutes per call. **(3) TMC + CM + TAU**: Plus incentives for TMC attendance. Participants in TMC and TMC+CM received a brief (40 minutes) HIV intervention. About 20 % of patients randomized to TMC and TMC+CM failed to complete the initial orientation sessions and therefore did not receive any HIV risk reduction interventions.	N=321 adults (age 18-65) with a lifetime diagnosis of **cocaine** dependence (DSM-IV) who used cocaine in the prior 6 months and who completed 2 weeks of intensive outpatient treatment. Approximately 83% had current cocaine dependence, 39% had current alcohol dependence	**Cocaine use**: NSD between groups overall. Among those who used cocaine at intake or early in treatment, less use in TMC+CM than TAU group (OR= 0.55 [0.31, 0.95]). NSD between groups among those abstinent at baseline. **HIV sex-risk**: NSD between groups in risk reduction from baseline at 6 to 24 months. For people with no cocaine use at baseline, TAU experienced greater sex-risk reductions than TMC ($p < .01$) and TMC+CM ($p < .001$). NSD among participants with cocaine-positive baseline UDT.	NCT00685659 Also see Continuing Care and Telehealth The three treatment conditions are effective in reducing HIV sex-risk. TMC with HIV risk-reduction components is unnecessary for cocaine-dependent clients who stop using cocaine early in treatment.
Shoptaw 2005[41]	RCT	48 group sessions of (1) GCBT: Gay-specific CBT integrating	N= 162 treatment seeking MSM with **MaUD** (SCID-verified)	Retention 80% at 6 months **Sexual risk behavior** GCBT group had a greater reduction in unprotected receptive	In Pantalone 2020[12] and Colfax 2010[19]

	16 weeks, 6 & 12-month follow-up USA Outpatient	relevant cultural aspects of MA use by gay and bisexual men with matrix model CBT (Rawson et al., 1995). Included skills for reducing sexual risk behaviors. (2) CBT Matrix Model alone (3) CM alone (4) CM+CBT Matrix Model	(61% HIV+, 80% White)	anal intercourse compared to the other groups at 1 month ($\chi 2$ (3) = 6.75, p < .01), but NSD between groups at later follow-ups. **Stimulant use:** CM > CBT on percent of MA negative urine samples during the study (p < .01). **Continuous stimulant abstinenc**e: Longest period (in weeks) of consecutive MA metabolite-negative samples during the trial • CM > CBT (mean 5.1 vs 2.1 respectively) • No difference between CM and CM+CBT (mean=7) • GCBT **Stimulant abstinence**: Percent of meth-negative urine samples collected • No difference between CM and CBT at 6- or 12-month follow-up. • No difference between CM and CM+CBT at 6- or 12-month follow-up. • GCBT **Duration of treatment**: Weeks in treatment • CM > CBT (mean 12 vs 8.9 weeks respectively) • No difference between CM and CM+CBT (mean=13.3) • GCBT	Also see EtDT LGBT, EtDT Behav CM
Shoptaw 2008[42]	RCT 16 weeks, 12-month follow-up USA Outpatient	48 group sessions (1) **GCBT**: Gay-specific CBT (Shoptaw 2005) integrated relevant cultural aspects of MA use by gay and bisexual men with matrix model CBT	N= 128 treatment-seeking MSM age 18-65 with **stimulant** and/or **alcohol** use disorder (77% ATS, 15% cocaine, n=117).	**Treatment completion:** NSD bw groups at 16 weeks (total n=72, 56%). **Stimulant use (ATS + cocaine; UDT)**: GCBT had a greater percent of negative samples during treatment compared to GSST among primary substance stimulant participants (n=117, 85% vs 73%, p<0.05)	In Pantalone 2020[12] and Colfax 2010[19] Baseline differences between groups

		(Rawson et al., 1995). Included skills for reducing sexual risk behaviors. (2) **GSST**: Gay-specific social support integrated elements of peer-driven social model counseling with HIV health education/risk reduction groups.		**Amphetamine use (UDT, ASI)**: GCBT had a greater percent of negative samples during treatment compared to GSST among primary substance ATS participants (n=98, 92% vs 73%, $p<0.05$). During follow-up, GCBT group reported fewer days of ATS use compared to GSST ($\chi 2 = 6.57$, df =1, $p<.01$) **Cocaine use (UDT)**: 128 in percent of negative samples during treatment among primary substance cocaine participants (n=19, 56% vs 72%) **Sexual risk behavior (BQ)**: NSD between groups in risk reduction for all participants (n=128) and for participants whose primary substance is MA (n=98) in reported number of sexual partners and for the number of episodes of unprotected receptive and insertive anal intercourse with other than a primary partner in the prior 30 days. Could not calculate for primary substance cocaine (too small n).	in rate of IDU (higher in GSST) and initial UDT- (higher in GCBT).

ART = anti-retroviral therapy

ASI = Addiction Severity Index

BQ = behavioral questionnaire (Chesney, Chambers, & Kahn, 1997)

PHQ = Patient Health Questionnaire (PHQ) (Spitzer, Korenke, & Williams, 1999)

UAI = Unprotected anal intercourse

UIAI = Unprotected insertive anal intercourse

Existing Guidelines

Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016.

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Unhealthy Drug Use: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(22):2301. doi:10.1001/jama.2020.8020

United Nations Office on Drugs and Crime. *Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives*. United Nations Office on Drugs and Crime (UNODC); 2019.
United Nations Office on Drugs and Crime, World Health Organization (WHO), and Joint United Nations Programme on HIV/AIDS (UNAIDS). *HIV prevention, treatment, care and support for people who use stimulant drugs*; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf
Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):192. doi:10.15585/mmwr.rr7004a1

Non-systematic Reviews

Source	Recommendation	Comments
Chan 2022[43]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE • all patients should be encouraged to use safe sex practices, such as routine condom use	
Rigoni 2018[2]	Speed Limits: Harm Reduction for People Who use Stimulants • "To a certain extent, prevention of sexual risks is no different for people who use stimulant drugs than for other drug using populations. In any case, sexual health risk prevention should cover: free access to condoms and lubricant, information about STIs and HIV, low-threshold access to HIV and STI testing and treatment, contraception and pregnancy testing and counselling, talking about sexual risk, and developing a plan for self-control over harmful behaviours. Furthermore, addressing sexual and physical violence, transactional and commercial sex, abusive relationships, and other issues related to sexual risk behaviours is also important (Pinkham and Stone 2015)." (Rigoni et al., 2018, p. 28) "Some sexual risks, as well as the responding harm reduction and prevention measures, apply more specifically to PWUS." (Rigoni et al., 2018, p. 28) • "Stimulants tend to dry mucous membranes and decrease sensitivity, increasing the chances of longer and more intense sex. Therefore, PWUS should use plenty of lubricant. This is especially true for PWUS who make use of stimulants to facilitate and improve sexual activity, such as male PWUS in the chemsex scene." (Rigoni et al., 2018, p. 28) Chemsex (p. 28) "professionals and people involved in chemsex argue in favour of integrating chemsex assessments and referrals into existing care pathways (Knoops et al. 2015a; Pufall et al. 2018; Bakker and Knoops 2018)." (Rigoni et al., 2018, p. 29) "provide chemsex services within MSM-friendly sexual health clinics or services, instead of referring men to existing drug services. Some such specialised services have already started emerging in the USA, Australia and the UK (Frankis and Clutterbuck 2017; Knoops et al. 2015a)." (Rigoni et al., 2018, p. 29) "offering direct contact with chemsex users, and providing non-judgmental information on harm reduction and (sexual) health promotion (Adam Bourne, Ong, and Pakianathan 2018)." (Rigoni et al., 2018, p. 29)	Systematic review, not appraised

Additional Resources from Guidelines

Source	Resources	Comments
	Substance Abuse and Mental Health Services Administration. (2020j). Prevention and treatment of HIV among people living with substance use and/or mental disorders. Publication No. PEP20-06-03-001. Substance Abuse and Mental Health Services Administration.	
UNDOC/WHO 2019	The website "Sleaze without consequences", created by the Dutch organizations Soa Aids Netherland and Mainline, provides information on reducing the risks of hepatitis, HIV and other STIs, and safer-sex information for men who have sex with men engaging in ChemSex.	
CDC 2021	**Sexually Transmitted Infections Treatment Guidelines, 2021 (Workowski 2021)** • Behavioral counseling and other STI prevention strategies (https://www.cdc.gov/std/prevention); compendium of evidence-based behavioral counseling interventions that have been shown to reduce STI acquisition or increase safer sexual behaviors (https://www. cdc.gov/hiv/research/interventionresearch/compendium/rr/ complete.html). • Training in client-centered counseling and motivational interviewing is available through the STD National Network of Prevention Training Centers (https://www.nnptc.org).	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients may be uncomfortable	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No evidence ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies

***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. Education is an important component of change and relatively easy to implement; the importance of patient education is readily supported across a range of other medical conditions.

Subgroup Considerations

Patients with high readiness to change may have better outcomes.

Implementation Considerations

Requires combining with other HR activities. Requires clinician knowledge and comfort with harm reduction principles

References

1. Vu NTT, Maher L, Zablotska I. Amphetamine-type stimulants and HIV infection among men who have sex with men: implications on HIV research and prevention from a systematic review and meta-analysis. *J Int AIDS Soc*. 2015;18(1):19273. doi:10/f62st3
2. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
3. Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

4. Khan MR, Berger A, Hemberg J, O'Neill A, Dyer TP, Smyrk K. Non-injection and injection drug use and STI/HIV risk in the United States: the degree to which sexual risk behaviors versus sex with an STI-infected partner account for infection transmission among drug users. *AIDS Behav*. 2013;17(3):1185-1194. doi:10.1007/s10461-012-0276-0
5. Booth RE, Kwiatkowski CF, Chitwood DD. Sex related HIV risk behaviors: differential risks among injection drug users, crack smokers, and injection drug users who smoke crack. *Drug Alcohol Depend*. 2000;58(3):219-226. doi:10.1016/s0376-8716(99)00094-0
6. Hittner JB. Meta-analysis of the association between methamphetamine use and high-risk sexual behavior among heterosexuals. *Psychol Addict Behav*. 2016;30(2):147-157. doi:10.1037/adb0000162
7. United Nations Office on Drugs and Crime, World Health Organization (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS). *HIV Prevention, Treatment, Care and Support for People Who Use Stimulant Drugs*. United Nations Office on Drugs and Crime; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf
8. Henderson JT, Senger CA, Henninger M, Bean SI, Redmond N, O'Connor EA. Behavioral Counseling Interventions to Prevent Sexually Transmitted Infections: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;324(7):682. doi:10.1001/jama.2020.10371
9. Tran MTN, Luong QH, Le Minh G, Dunne MP, Baker P. Psychosocial Interventions for Amphetamine Type Stimulant Use Disorder: An Overview of Systematic Reviews. *Front Psychiatry*. 2021;12:512076. doi:10.3389/fpsyt.2021.512076
10. Radfar SR, Mohsenifar S, Noroozi A. Integration of Methamphetamine Harm Reduction into Opioid Harm Reduction Services in Iran: Preliminary Results of a Pilot Study. *Iran J Psychiatry Behav Sci*. 2017;11(2). doi:10.5812/ijpbs.7730
11. Strona FV, McCright J, Hjord H, et al. The acceptability and feasibility of the Positive Reinforcement Opportunity Project, a community-based contingency management methamphetamine treatment program for gay and bisexual men in San Francisco. *J Psychoactive Drugs*. 2006;Suppl 3:377-383. doi:10.1080/02791072.2006.10400601
12. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
13. Elkbuli A, Polcz V, Dowd B, McKenney M, Prado G. HIV prevention intervention for substance users: a review of the literature. *Subst Abuse Treat Prev Policy*. 2019;14(1):1. doi:10.1186/s13011-018-0189-7
14. Knight R, Karamouzian M, Carson A, et al. Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine: A systematic review. *Drug Alcohol Depend*. 2019;194:410-429. doi:10.1016/j.drugalcdep.2018.09.023
15. Fischer B, Blanken P, Da Silveira D, et al. Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: a comprehensive narrative overview of English-language studies. *Int J Drug Policy*. 2015;26(4):352-363. doi:10/f66rht
16. Meader N, Semaan S, Halton M, et al. An International Systematic Review and Meta-analysis of Multisession Psychosocial Interventions Compared with Educational or Minimal Interventions on the HIV Sex Risk Behaviors of People Who Use Drugs. *AIDS Behav*. 2013;17(6):1963-1978. doi:10.1007/s10461-012-0403-y
17. Johnson WD, Rivadeneira N, Adegbite AH, et al. Human Immunodeficiency Virus Prevention for People Who Use Drugs: Overview of Reviews and the ICOS of PICOS. *J Infect Dis*. 2020;222(Suppl 5):S278-S300. doi:10.1093/infdis/jiaa008
18. Meader N, Li R, Jarlais DCD, Pilling S. Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users. *Cochrane Database Syst Rev*. 2010;(1). doi:10.1002/14651858.cd007192.pub2
19. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *The Lancet*. 2010;376(9739):458-474. doi:10.1016/S0140-6736(10)60753-2
20. Carrico AW, Zepf R, Meanley S, Batchelder A, Stall R. Critical Review: When the Party is Over: A Systematic Review of Behavioral Interventions for Substance-Using Men Who Have Sex with Men. *J Acquir Immune Defic Syndr 1999*. 2016;73(3):299-306. doi:10.1097/QAI.0000000000001102

21. Johnson WD, Diaz RM, Flanders WD, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *Cochrane Database Syst Rev*. 2008;(3). doi:10.1002/14651858.cd001230.pub2
22. Hatch-Maillette MA, Harwick R, Baer JS, et al. Increasing substance use disorder counselors' self-efficacy and skills in talking to patients about sex and HIV risk: A randomized training trial. *Drug Alcohol Depend*. 2019;199:76-84. doi:10.1016/j.drugalcdep.2019.02.023
23. Carrico AW, Flentje A, Gruber VA, et al. Community-Based Harm Reduction Substance Abuse Treatment with Methamphetamine-Using Men Who Have Sex with Men. *J Urban Health*. 2014;91(3):555-567. doi:10.1007/s11524-014-9870-y
24. Carrico AW, Nation A, Gómez W, et al. Pilot trial of an expressive writing intervention with HIV-positive methamphetamine-using men who have sex with men. *Psychol Addict Behav J Soc Psychol Addict Behav*. 2015;29(2):277-282. doi:10.1037/adb0000031
25. Carrico AW, Gómez W, Siever MD, Discepola MV, Dilworth SE, Moskowitz JT. Pilot Randomized Controlled Trial of an Integrative Intervention with Methamphetamine-Using Men Who Have Sex with Men. *Arch Sex Behav*. 2015;44(7):1861-1867. doi:10.1007/s10508-015-0505-5
26. Herrmann ES, Heil SH, Sigmon SC, Dunn KE, Washio Y, Higgins ST. Characterizing and improving HIV/AIDS knowledge among cocaine-dependent outpatients using modified materials. *Drug Alcohol Depend*. 2013;127(1-3):220-225. doi:10/gn764n
27. Kurtz SP, Stall RD, Buttram ME, Surratt HL, Chen M. A randomized trial of a behavioral intervention for high risk substance-using MSM. *AIDS Behav*. 2013;17(9):2914-2926. doi:10.1007/s10461-013-0531-z
28. Landovitz RJ, Fletcher JB, Shoptaw S, Reback CJ. Contingency Management Facilitates the Use of Postexposure Prophylaxis Among Stimulant-Using Men Who Have Sex With Men. *Open Forum Infect Dis*. 2015;2(1). doi:10.1093/ofid/ofu114
29. Mansergh G, Koblin BA, McKirnan DJ, et al. An Intervention to Reduce HIV Risk Behavior of Substance-Using Men Who Have Sex with Men: A Two-Group Randomized Trial with a Nonrandomized Third Group. Kalichman SC, ed. *PLoS Med*. 2010;7(8):e1000329. doi:10.1371/journal.pmed.1000329
30. Mausbach BT, Semple SJ, Zians J, Patterson TL, Strathdee SA. Efficacy of a behavioral intervention for increasing safer sex behaviors in HIV-negative, heterosexual methamphetamine users: Results from the fast-lane study. A*nn Behav Med*. 2007a;34(3):263-274. doi:10.1007/BF02874551
31. Mausbach BT, Semple SJ, Strathdee SA, Zians J, Patterson TL. Efficacy of a behavioral intervention for increasing safer sex behaviors in HIV-positive MSM methamphetamine users: Results from the EDGE study. *Drug Alcohol Depend*. 2007b;87(2-3):249-257. doi:10.1016/j.drugalcdep.2006.08.026
32. Menza TW, Jameson DR, Hughes JP, Colfax GN, Shoptaw S, Golden MR. Contingency management to reduce methamphetamine use and sexual risk among men who have sex with men: a randomized controlled trial. *BMC Public Health*. 2010;10(1):774. doi:10.1186/1471-2458-10-774
33. Parsons JT, John SA, Millar BM, Starks TJ. Testing the efficacy of combined Motivational Interviewing and Cognitive Behavioral Skills Training to reduce methamphetamine use and improve HIV medication adherence among HIV-positive gay and bisexual men. *AIDS Behav*. 2018;22(8):2674-2686. doi:10.1007/s10461-018-2086-5
34. Safren SA, O'Cleirigh CM, Skeer M, Elsesser SA, Mayer KH. Project enhance: a randomized controlled trial of an individualized HIV prevention intervention for HIV-infected men who have sex with men conducted in a primary care setting. *Health Psychol Off J Div Health Psychol Am Psychol Assoc*. 2013;32(2):171-179. doi:10.1037/a0028581
35. Sherman SG, Sutcliffe C, Srirojn B, Latkin CA, Aramratanna A, Celentano DD. Evaluation of a peer network intervention trial among young methamphetamine users in Chiang Mai, Thailand. *Soc Sci Med*. 2009;68(1):69-79. doi:10.1016/j.socscimed.2008.09.061
36. Zule WA, Poulton WE, Coomes CM, et al. Results of a Pilot Study to Reduce Methamphetamine Use and Sexual Risk Behaviors Among Methamphetamine-Using Men Who Have Sex with Men (MSM) Not Currently in Treatment. *J Psychoactive Drugs*. 2012;44(5):351-358. doi:10.1080/02791072.2012.736794
37. Reback CJ, Shoptaw S. Development of an evidence-based, gay-specific cognitive behavioral therapy intervention for methamphetamine-abusing gay and bisexual men. *Addict Behav*. 2014;39(8):1286-1291. doi:10.1016/j.addbeh.2011.11.029
38. McDonell MG, Srebnik D, Angelo F, et al. Randomized Controlled Trial of Contingency Management for Stimulant Use in Community Mental Health Patients With Serious Mental Illness. *AJP*. 2013;170(1):94-101. doi:10.1176/appi.ajp.2012.11121831

39. McKay JR, Van Horn DH, Lynch KG, et al. An adaptive approach for identifying cocaine dependent patients who benefit from extended continuing care. *J Consult Clin Psychol*. 2013;81(6):1063. doi:10.1037/a0034265
40. Wimberly AS, Ivey M, Rennert L, McKay JR. Effect of Continuing Care for Cocaine Dependence on HIV Sex-Risk Behaviors. *AIDS Behav*. 2017;21(4):1082-1090. doi:10.1007/s10461-016-1434-6
41. Shoptaw S, Reback CJ, Peck JA, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-134. doi:10/bkdpqf
42. Shoptaw S, Reback CJ, Larkins S, et al. Outcomes using two tailored behavioral treatments for substance abuse in urban gay and bisexual men. *J Subst Abuse Treat*. 2008;35(3):285-293. doi:10.1016/j.jsat.2007.11.004
43. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 60. Prevention Naloxone

Recommendation: For patients who use stimulants from non-medical sources, or are socially engaged with others who do, clinicians should prescribe or distribute overdose reversal medications (eg, naloxone) or refer patients to where they can obtain these medications in the community.

Clinical Question Summary

Clinical Question	What are effective strategies for distributing naloxone to patients with StUD?
Population	patients who use stimulants from non-medical sources
Intervention	Strategies for distributing naloxone to patients who use stimulants from nonmedical sources
Comparison	No intervention
Main Outcomes	Reduced risk of overdose (long term)
Setting	Clinical settings
Background & Definitions	Notes: • "Our views on the contribution of cocaine to drug overdoses have undergone a rapid shift. In 2017, a reported 52% of all fatal drug overdoses in the United States involved cocaine (n= 70237) [15]. While adulteration with synthetic opioids, such as fentanyl, may contribute to growing overdose rates [16], recent data indicate that one-quarter of cocaine overdose deaths were without any opioid involvement [15]. In Europe, stimulant overdoses account for a smaller proportion of drug-related deaths, but these rates vary widely by country [4]." (Brandt 2021, p2)[1] • "Recent increases in stimulant-involved overdose deaths in the US have been well-documented, although partially attributed to the coinvolvement of opioids in many of the overdose deaths involving stimulants (Hoots, Vivolo-Kantor, & Seth, 2020; Kariisa, Scholl, Wilson, Seth, & Hoots, 2019; McCall Jones, Baldwin, & Compton, 2017). Several analyses have concluded that synthetic opioids have largely driven the recent increases in cocaine-involved overdose mortality, while increases in overdose deaths involving psychostimulants (eg, methamphetamine) may be only partially explained by co-involvement of opioids (Hoots et al., 2020; Kariisa et al., 2019). Opioids were reported in 72.7% of cocaine-involved overdose deaths and 50.4% of psychostimulant-involved overdose deaths nationwide in 2017 (Kariisa et al., 2019), yet it is unclear if this level of opioid co-involvement in stimulant-involved deaths is observed across all racial/ethnic groups." (Cano 2021, p2)[2] • "Significant increases in drug overdose mortality rates from 2017 to 2018 were observed for NH Black males, Hispanic males, and NH Blacks aged 65 and older, as well as for overdoses involving psychostimulants (in all racial/ethnic groups) and cocaine (in NH Blacks and Hispanics). the level of opioid co-involvement in stimulant-involved overdose deaths also varied by race/ethnicity." (Cano 2021, p1)[2] • "Most participants believed that methamphetamine could help prevent and/or reverse an opioid-related overdose. Nearly half had personally used it to help manage overdose risks related to NPF. These beliefs were embedded in a lay understanding of how methamphetamine works to stimulate the cardiovascular system." (Daniulaityte 2022, p1)[3]

	• "Alerting emergency medical services (EMS) is an OOPP-recommended action that is of particular significance because naloxone has a short duration of action and individuals may experience medical complications related to recurring inadequate respiration. In addition, notification of EMS may simultaneously alert police to respond to the scene." (Clark 2014, p161)[4]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Overdose recovery	N/A	Meta-analysis: Giglio 2015[5] (Not assessed)	Naloxone administration by bystanders was associated with a significantly increased odds of recovery compared with no naloxone administration in 4 uncontrolled studies (OR = 8.58 [3.90, 13.25), p<0.001; I^2=92%, p<0.001). • Galea 2006 (cohort, quality 7/8); Lankenau 2013 (cross-sectional, quality 6/8); McAuley 2010 (cohort, quality 7/8); Strang 2008 (prospective cohort, quality 7/8)	Effectiveness of bystander naloxone administration and overdose education programs. Quality appraisal adapted from Jinks [6] rated on eight items. Perfect score is 8/8.
		Systematic review: Clark 2014[4]	"Eleven studies [out of 15] reported 100% survival rate post–naloxone administration; the remaining articles reported a range of 83% to 96% survival. In 2 articles that observed lower rates of survival, this finding was confounded by a greater number of unknown overdose outcomes (Markham Piper et al., 2008; Enteen et al., 2010)." (p. 155)	Community opioid overdose prevention and naloxone distribution programs. All non-random studies, "fair" quality.
Naloxone administration	N/A	Systematic review: Clark 2014[4]	"Naloxone was used successfully by participants in all but one reviewed study, for a total of 1949 reported naloxone administrations across 18 programs." (p. 155)	Community opioid overdose prevention and naloxone distribution programs. All non-random studies, "fair" quality.
Opioid-related ED visit	N/A	Systematic review: Haegerich 2019[7]	"We determined the quality of evidence to be low given study designs, despite the preponderance of evidence of naloxone as a vital clinical tool and consensus of the large volume of findings." (p. 8) "A time series analysis with concurrent controls identified that overdose death rates were significantly reduced in communities with opioid education and naloxone distribution (OEND) programs	Opioid focus

			compared to communities without these programs (Walley et al., 2013a).” (p. 8) “In a nonrandomized intervention study, Coffin et al. (2016) documented a decrease in opioid-related ED visits after providers and clinic staff were trained in naloxone prescribing, with a focus on indications for prescribing, language to use with patients, formulations, payer coverage, and naloxone use. However, in a randomized trial, Banta-Green et al. (2011) conducted overdose education, brief counseling, and naloxone prescription for patients at elevated risk for an overdose after an ED visit and found that overdose events did not significantly differ between intervention and control participants.” (p. 8)	
Overdose knowledge	N/A	Meta-analysis: Giglio 2015[5] (Not assessed)	Overdose education participants had higher naloxone administration, overdose recognition, and overdose response knowledge compared to untrained participants in 5 studies (1 RCT, 4 uncontrolled) (standardized mean difference = 1.35 [0.92, 1.77], $p<0.001$; $I^2=0\%$, $p=0.91$). • Gaston 2009 (cohort, quality 7/8); Green 2008 (cross-sectional, quality 6/8); Jones 2014 (cohort, quality 6/8); McAuley 2010 (cohort, quality 7/8); Williams 2014 (RCT, quality 8/8)	Effectiveness of bystander naloxone administration and overdose education programs. Quality appraisal adapted from Jinks [6] rated on eight items. Perfect score is 8/8.
Naloxone prescribing acceptability	N/A	Systematic review: Behar 2018[8] (Not assessed)	“We found that prescribing naloxone in primary care settings is generally an acceptable and feasible intervention among both providers and patients” (p. 8). “Six articles directly assessed providers’ willingness to prescribe naloxone. The two earliest published articles reported the highest degree of provider resistance to naloxone prescribing. One study, published in 2003, stated that 37% of respondents would not be willing to prescribe naloxone while another study, published in 2006, stated that 54% of respondents would not prescribe naloxone. In contrast, the two most recent studies, published in 2016 and 2017, indicated that 90% and 99% of prescribers were willing to prescribe naloxone, respectively” (p. 3).	Acceptability and feasibility of naloxone prescribing in primary care settings
Naloxone acceptability	N/A	Systematic review: Behar 2018[8] (Not assessed)	3 studies. “Studies also confirmed that the majority of patients were comfortable and willing to administer naloxone if needed” (p. 6).	Acceptability and feasibility of naloxone prescribing in primary care settings
Naloxone prescribing feasibility	N/A	Systematic review: Behar 2018[8] (Not assessed)	6 studies. “Studies assessing feasibility demonstrated that naloxone prescribing in primary care practice is feasible” (p. 4).	Acceptability and feasibility of naloxone prescribing in primary care settings

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Dwyer 2015[9]				Dwyer et al. (2015) conducted a comparative study using a with non-randomised controls using a telephone survey. They attempted contact with patients who had received overdose education (n = 359), or overdose education plus intranasal THN (n = 59) in the ED. 11–12 months post initial ED visit (37 of whom received THN), 19 % of the naloxone and 29 % of the education only group reported a non-fatal overdose (p = 0.47). It is of note that 32 % of the THN group and none of the education group used a naloxone kit to reverse a witnessed overdose. The THN provision was not randomised as it was dependent on staff availability and patient preference.	
Walley 2013b[10]	interrupted time series analysis		N=	areas in Massachusetts with higher levels of enrollment in OOPPs had lower rates of opioid-related overdose death after controlling for other factors.	In Clark 2014[4]

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[11]	Harm Reduction in Health Care Settings Harm reduction for stimulant use • Owing to fentanyl being found in stimulant supplies we recommend universal fentanyl precautions by carrying naloxone • Prevent opioid overdose fatalities by prescribing naloxone to those who use opioids, stimulants, or any emerging substance at risk of fentanyl contamination. Opioid Overdose Prevention – Naloxone • Even in the era of fentanyl and fentanyl analogues (FFA), it is still recommended to use 1 to 2 standardized doses of 4 mg intranasal naloxone or 0.4 mg/1 mL intramuscular naloxone, to reverse an opioid overdose successfully; however, sometimes additional doses might be still necessary. • It is important for clinicians and PWUD to know that naloxone is a safe35 and effective way to reverse an opioid overdose.38 In the absence of opioids, naloxone will neither cause harm nor worsen respiratory depression.35,36 The most common side effect of naloxone is precipitated withdrawal.35,36	
Stone & Shirley-Beavan 2018[12]	The global state of harm reduction 2018 • "In an evaluation of community opioid overdose prevention, researchers found 83-100% survival rates post-naloxone treatment, demonstrating that non-medical bystanders trained in community opioid prevention techniques were effectively able to administer naloxone.[61]" (Stone and Shirley-Beavan, 2018, p. 22) ○ 61. EMCDDA (2017) Health and Social Responses to Drug Problems: A European Guide. Lisbon: European Monitoring Centre for Drugs and Drug Addiction.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Strong evidence, indirect		☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	When naloxone is available, other causes are minimized Person might have collapsed for other reasons, bystanders less likely to call 911	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
High quality, indirect		☐ No evidence ☐ Very low ☐ Low ☐ Moderate ☒ High

***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Access to overdose reversal medications is likely to be beneficial with relatively little risk

Subgroup Considerations

None noted

Implementation Considerations

Access still an issue in some areas

References

1. Brandt L, Chao T, Comer SD, Levin FR. Pharmacotherapeutic strategies for treating cocaine use disorder-what do we have to offer? *Addict Abingdon Engl*. 2021;116(4):694-710. doi:10.1111/add.15242
2. Cano M. Racial/ethnic differences in US drug overdose mortality, 2017-2018. *Addict Behav*. 2021;112:106625. doi:10/gn76f2
3. Daniulaityte R, Silverstein SM, Getz K, Juhascik M, McElhinny M, Dudley S. Lay knowledge and practices of methamphetamine use to manage opioid-related overdose risks. *Int J Drug Policy*. 2022;99:103463. doi:10.1016/j.drugpo.2021.103463
4. Clark AK, Wilder CM, Winstanley EL. A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs. *J Addict Med*. 2014;8(3):153-163. doi:10.1097/ADM.0000000000000034
5. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol*. 2015;2(1):10. doi:10.1186/s40621-015-0041-8
6. Jinks A, Cotton A, Rylance R. Obesity interventions for people with a learning disability: an integrative literature review. *J Adv Nurs*. 2011;67(3):460-471. doi:10.1111/j.1365-2648.2010.05508.x
7. Haegerich TM, Jones CM, Cote PO, Robinson A, Ross L. Evidence for state, community and systems-level prevention strategies to address the opioid crisis. *Drug Alcohol Depend*. 2019;204:107563. doi:10.1016/j.drugalcdep.2019.107563
8. Behar E, Bagnulo R, Coffin PO. Acceptability and feasibility of naloxone prescribing in primary care settings: A systematic review. *Prev Med*. 2018;114:79-87. doi:10.1016/j.ypmed.2018.06.005
9. Dwyer R, Fraser S, Dietze P. Benefits and barriers to expanding the availability of take-home naloxone in Australia: A qualitative interview study with service providers. *Drugs (Abingdon Engl)*. 2016;23(5):388-396.
10. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346(jan30 5):f174-f174. doi:10.1136/bmj.f174
11. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002
12. Stone K, Shirley-Beavan S. *The Global State of Harm Reduction 2018*. Harm Reduction International; 2018. Accessed November 3, 2022. https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf

Table 61. Prevention Drug Checking

Recommendation:
Clinicians should recommend that patients perform comprehensive drug checking, including testing with fentanyl test strips, every time they get a new batch of stimulants from non-medical sources, and review the technique for using fentanyl test strips when permitted by state law.

Clinical Question Summary

Clinical Question	Is drug checking an effective strategy for reducing harms related to StUD?
Population	People who use drugs
Intervention	Drug checking (DC) by consumers and promoting the use of drug-checking services (DCS)
Comparison	TAU (absence)
Main Outcomes	Reduced risk for overdose (long term)
Setting	Clinical settings
Background & Definitions	Comprehensive drug checking Notes: • An increasing number of specimens submitted for testing by health care professionals as part of routine care are positive for cocaine or methamphetamine were also positive for nonprescribed fentanyl (LaRue 2019)[1]. • "Single-use urine fentanyl test strips purchased from BTNX Inc. were utilized, having already been employed for on-site drug checking (Tupper et al., 2018). In the drug checking context, these are used to test a small portion of a substance diluted in water rather than the original intended use on urine samples. This method of using fentanyl test strips is off-label, and thus instructions for use were created and provided by study staff, rather than the manufacturer. While a novel utilization, the use of test strips in this way has been previously described (Krieger et al., 2018b; Tupper et al., 2018). Their detection limit for fentanyl is 130ng/ml and they are able to detect various fentanyl analogues (McCrae et al., 2020; Sherman & Green, 2018). Recent data suggests the sensitivity of these immunoassay strips for detecting fentanyl is 87.5%, while the specificity is 95.2% (Ti et al., 2020)." (Klaire 2022, p2)[3] • Positive fentanyl immunoassay tests underwent reflex chromatography confirmation testing during 2016 in a Massachusetts urban safety-net hospital (Kerensky 2021)[4]. Of 11,873 urine samples, 10.4% of samples screened fentanyl positive and 8.8% were confirmed fentanyl positive. The positive predictive value of a positive urine fentanyl screen was 85.7%.
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/ Important Outcomes				
Overdose	N/A	Systematic review: Maghsoudi 2022[5]	1 study linked intended behaviors to observed health outcomes for PWUD accessing DCS. • Karamouzian 2018 (n=1411 Canada PWID cross section) 36% reported intending to use less than usual if fentanyl detected pre-use. more likely to report the intention to use a smaller quantity than usual when fentanyl was detected by DCS (OR=9.36 [4.25, 20.65]). Those intending to use less than usual were less likely to overdose (OR=0.41 [0.18, 0.89]).	DCS = Drug Checking Services
Drug use behavior	N/A	Systematic review: Maghsoudi 2022[5]	10 studies reported on the influence of drug checking analysis results on drug use behavior. **Author conclusion:** Drug checking services appear to influence the behavior of people who use drugs	
Drug use intentions	N/A	Systematic review: Maghsoudi 2022[5]	13 studies of PWUD consistently reported greater intention to not use the analyzed substance if results were unexpected or 'questionable'/ 'suspicious' **Author conclusion:** Drug checking services appear to influence behavioral intentions to use drugs.	
Adverse effects/ consequences	N/A	Systematic review: Giulini 2022[6]	"Evidence does not support the view that offering drug-checking services (DCS) at a festival will result in drug use by people who have never used drugs or that a DCS will increase use among people who already use drugs (Hollett and Gately 2019; Murphy, Bright, and Dear 2021)." (Giulini et al., 2022, p. 2)	Focus on "recreational" drug use population (eg, festival attendees).

[i]: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Individual Studies

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Goodman-Meza 2022[7]	Mixed methods–survey, interview, observation Dec 2020--Feb 2021 Mexico	Fentanyl testing of substances provided	N=30 women who used drugs at an unsanctioned safe consumption site. Participants reported bringing black tar heroin (28), brown heroin (1), and methamphetamine (1).	**Acceptability**: Fentanyl testing was acceptable **Injection behavior**: Among participants with positive fentanyl tests (n=15), 7 (47%) used less of the substance, 1 did not use the substance, and 7 (47%) did not change their behavior (ie, used as originally intended).	Behavior change is hampered by the inability to find substances free of fentanyl
Klaire 2022[3]	Cross-sectional survey April-July 2019 Canada	Take-home fentanyl test strips and training on how to conduct a test and interpret the result.	N= 218 (62% male) people who use drugs recruited from one of 10 sites providing on-site drug checking using fentanyl test strips. About 20% of samples tested were expected to contain stimulants.	**Drug use behavior:** When fentanyl was detected, 27% reported behavior change that was considered safer/positive: use less/use more slowly (n=45), use with someone else (n=26), use at an OPS/SCS (n=9), not use at all (n=7), or have someone check on them (n=4). **Acceptability:** Greater than 95% of participants stated they would use fentanyl test strips again.	"The pilot program was operated for four months to test enough opioid samples. This timeframe did not allow for the collection of sufficient stimulant samples." (p. 3)
Reed 2021[8]	Qualitative interview Jan 2019-Jan 2020 USA	N/A	N=15 adults (18+) recruited from an overdose education and naloxone distribution (OEND) program delivered in jail (n=11) or to recently released individuals (n=7) who reported regular use of **stimulants** before and after their most recent incarceration. All participants were living with HIV.	**Acceptability**: Stimulant users would use fentanyl test strips if available.	
Tupper 2018[9]	Pilot program Nov 2017 – April 2018 Canada	Drug checking of substances provided. Fentanyl immunoassay strip vs Fourier transform infrared	N= 1714 samples offered by a sub-set of self-selected clients of one of two supervised consumption services (SCS) in downtown Vancouver.	Of 256 samples expected to be speed or MA, 225 (87.9%) contained amphetamine or MA, and 15 (5.9%) tested positive for fentanyl.	

		(FTIR) spectrometer test to identify fentanyl		Of 140 samples expected to be "cocaine" or "crack", 128 (91.4%) contained actual cocaine hydrochloride or freebase, and 3 (2.1%) tested positive for fentanyl.	

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[2]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE • All patients with stimulant use should be counseled on the risk of opioid exposure • Test drugs with fentanyl test strips before use (opioids and stimulants) • Counsel patients on risk of false-negatives • Owing to fentanyl being found in stimulant supplies we recommend universal fentanyl precautions by using fentanyl test strips to test drug supplies. OPIOID OVERDOSE PREVENTION - Fentanyl Test Strips • Clinicians should counsel patients on adjusting behavior in the presence of a positive FTS test, as well as the real risk of false-negative tests. • Risk reducing behavior changes if there is a positive result include using smaller amounts or test doses, using around someone else, ensuring availability of naloxone, or injecting slowly. • Concerns regarding test accuracy – It is uncertain whether FTS can detect other rapidly emerging high-potency synthetic opioids (HPSO) • Risks associated with false-negative tests – False-negatives can also occur when the sample tested is too dilute.	
Giulini 2022[6]	A Systematized Review of Drug-checking and Related Considerations for Implementation as A Harm Reduction Intervention • Fixed-site services developed for monitoring and analysis purposes supported by accompanying intervention services similar to the Netherlands' DIMS have enormous potential to engage hard-to-reach groups, influence behaviors, and minimize harm. • Each interaction with service users should be accompanied by prevention, education, and harm reduction.	

Fleming 2020[10]	Stimulant safe supply: a potential opportunity to respond to the overdose epidemic • Drug-checking technologies (DCT) • Supervised consumption sites (SCS) • "Provision of a safe supply (ie, legal, nonadulterated, of known quality, and with user agency in consumption practices) of stimulants are urgently needed as part of a more comprehensive response to the overdose crisis." (p. 3) • "Access to a consistent supply of stimulants of known quality can possibly lead to the same improved health outcomes observed among participants in injectable hydromorphone and diacetylmorphine interventions, such as reductions in abscesses [33], transmission of infectious disease (eg, hepatitis C, HIV) [34], early mortality [35], and reduced engagement with law enforcement [36]." (p. 4)	
Rigoni 2018[11]	Speed Limits: Harm Reduction for People Who use Stimulants	
Stone & Shirley-Beavan 2018[12]	The global state of harm reduction 2018 • "DanceSafe is one popular harm reduction and peer-based education intervention which offers a drug-checking service (EcstatsyData.org) and the only publicly accessible laboratory analysis of ecstasy data in the US.[52] It also provides testing kits to purchase online, including for methamphetamines, opioids, MDMA and psychedelics such as LSD, as well as fentanyl test strips. [52]" (p. 118)	

Other Resources

Source	Resource	Comments
	Look for something out of Rhode Island (Tracy Green)	
	Resource for comprehensive drug checking methods - Dance Safe	
	Boston Public Health Commission's Access Harm Reduction Overdose Prevention and Education Program Participant Guide (https://www. bphc.org/whatwedo/Recovery-Services/servicesfor-active-users/Documents/Client%20Manual%20 FINAL.pdf). From SAMHSA (2021)	Check this for drug checking info
Stone & Shirley-Beavan 2018[12]	Dance Safe (2018) Dance Safe: Promoting Health and Safety Within the Electronic Music Community. Dance Safe. Available from: https://dancesafe.org/about-us/.	
Stone & Shirley-Beavan 2018[12]	Sherman S, Green T (2018) Detecting Fentanyl. Saving Lives. John Hopkins Bloomberg School of Public Health. Available from: http://americanhealth. jhu.edu/fentanyl.	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
1 systematic analysis found persons with drug use would use less if fentanyl was detected before use. At least 1 study found that accessing comprehensive drug checking services was associated with reduced overdose rate.	The findings varied by population studied (eg, festivals, IDU) and is extrapolated from opioid data, although stimulant users were not explicitly excluded. Stimulant users are expected to be in the population that would benefit from comprehensive drug checking programs.	☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No undesirable clinical effects were found. At least 1 systematic review among "recreational" drug use population (eg, festival attendees) did not result in increased drug use.	Errors in testing/results were not reported. Probably more likely to get false positives than false negatives, but this is unlikely to result in adverse outcomes. However, inaccurate results may lead to mistrust in the program.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
Data to show that people to change their behavior a small to moderate amount depending on population.	When available	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	Low or moderate	☐ No evidence ☐ Very low ☐ Low ☒ Moderate

		☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Cost. Varies based on availability of testing sites. More common in urban settings.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Fentanyl Test Strips: Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
One cross-sectional study found a moderate change in behavior		☐ None ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Errors in testing/results were not reported. Probably more likely to get false positives than false negatives, but this is unlikely to result in adverse outcomes. However, inaccurate results may lead to mistrust in the program.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Given that the intervention may reduce the significantly bad outcome of opioid overdose, the intervention is substantially favored despite moderate effect size.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No evidence ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
At least 2 studies found that stimulant users would use fentanyl test strips if available.	Decriminalization of fentanyl test strips is expanding in the US and is critical to the success of the intervention.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Cost. This could involve a lot of fentanyl test strips. Although they are inexpensive the cost may add up. It is unlikely that the intervention will be implemented successfully if the test strips are not freely available. Distribution – will they be distributed through the existing harm reduction infrastructure?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Drug checking is becoming a standard harm reduction practice. Some evidence was found that people who use substances would use less if fentanyl was detected before use

Subgroup Considerations

None noted

Implementation Considerations

When using drug checking kits, it is important that patients follow package instructions to avoid false negatives Proper technique is important to reduce false negatives and false positive results.

References

1. LaRue L, Twillman RK, Dawson E, et al. Rate of Fentanyl Positivity Among Urine Drug Test Results Positive for Cocaine or Methamphetamine. *JAMA Netw Open*. 2019;2(4):e192851. doi:10.1001/jamanetworkopen.2019.2851
2. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002
3. Klaire S, Janssen RM, Olson K, et al. Take-home drug checking as a novel harm reduction strategy in British Columbia, Canada. *Int J Drug Policy*. 2022;106:103741. doi:10.1016/j.drugpo.2022.103741
4. Kerensky T, LaRochelle M, Fan S, Kosakowski S, Wason K, Walley A. Non-prescription Fentanyl Positive Toxicology: Prevalence, Positive Predictive Value of Fentanyl Immunoassay Screening, and Description of Co-substance Use. *J Addict Med*. 2021;15(2):150-154. doi:10/gn76k6
5. Maghsoudi N, Tanguay J, Scarfone K, et al. Drug checking services for people who use drugs: a systematic review. *Addict Abingdon Engl*. 2022;117(3):532-544. doi:10.1111/add.15734
6. Giulini F, Keenan E, Killeen N, Ivers JH. A Systematized Review of Drug-checking and Related Considerations for Implementation as A Harm Reduction Intervention. *J Psychoactive Drugs*. 2022:1-9. doi:10.1080/02791072.2022.2028203
7. Goodman-Meza D, Arredondo J, Slim S, et al. Behavior change after fentanyl testing at a safe consumption space for women in Northern Mexico: A pilot study. *Int J Drug Policy*. 2022;106:103745. doi:10.1016/j.drugpo.2022.103745
8. Reed MK, Roth AM, Tabb LP, Groves AK, Lankenau SE. "I probably got a minute": Perceptions of fentanyl test strip use among people who use stimulants. *Int J Drug Policy*. 2021;92:103147. doi:10/gn756t

9. Tupper KW, McCrae K, Garber I, Lysyshyn M, Wood E. Initial results of a drug checking pilot program to detect fentanyl adulteration in a Canadian setting. *Drug Alcohol Depend*. 2018;190:242-245. doi:10.1016/j.drugalcdep.2018.06.020
10. Fleming T, Barker A, Ivsins A, Vakharia S, McNeil R. Stimulant safe supply: a potential opportunity to respond to the overdose epidemic. *Harm Reduct J*. 2020;17(1):6. doi:10.1186/s12954-019-0351-1
11. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*. 2018.
12. Stone K, Shirley-Beavan S. *The Global State of Harm Reduction 2018*. Harm Reduction International; 2018. Accessed November 3, 2022. https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf

Table 62. Prevention Overdose Prevention Sites

Recommendation: Clinicians should consider providing information to individuals about local overdose prevention sites when available.

Clinical Question Summary Table

Clinical Question	Is referral to SCS effective for reducing harms related to StUD?
Population	People who use stimulants
Intervention	Drug checking (DC) by consumers and promoting the use of drug-checking services (DCS)
Comparison	TAU (absence)
Main Outcomes	Reduced risk for overdose (long term)
Setting	Clinical settings
Background & Definitions	Notes • drug consumption rooms (DCRs) • safe injecting facilities (SIFs) • safe injecting sites (SISs) • overdose prevention site (OPS) • "Drug consumption rooms now operate in 11 countries around the world, with Belgium implementing its first facility in 2018. Australia, Canada, France, Spain, Switzerland and Norway have also opened new sites since 2016, with at least three further countries expected to open new facilities in 2019 (Ireland, Mexico and Portugal). In total, 117 sites operate at the time of reporting, compared with 90 in 2016. The increase since 2016 is mainly due to 24 new sites opening in Canada." (Stone & Shirley-Beavan 2018, p21)[1] • "While many DCRs are focused on people who use opioids and reducing the incidence of opioid overdose, others also serve populations who inject or inhale amphetamines and cocaine derivatives. For example, in the Netherlands, a number of facilities cater primarily to people who inhale drugs, in accordance with the landscape of drug use in that country. In these circumstances they ensure safe equipment is being used, and can serve as a link between people who use drugs and other health services." (Stone & Shirley-Beavan 2018, p22)[1]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **DCF**: Drug Consumption Facilities, **IDU**: Injection drug use/users, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MSIC**: Medically supervised injecting centers, **MSM**: Men who have sex with men, **N**: Number, **NSD**: No significant difference, **PWID**: People who inject drugs, **RCT**: Randomized Control Trial, **SMD**: Standard Mean Difference, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical Outcomes				
Overdose	N/A	Systematic review: Levengood 2021[2] (Not assessed)	**Conclusion:** Supervised injection facilities in the included studies were mostly associated with significant reductions in opioid overdose morbidity and mortality Sources: • **3 studies: Positive effect:** Significant reduction in opioid overdose morbidity and mortality associated with supervised injection facilities o Marshall 2011 (Canada) Review quality rating: Good o Salmon 2010 (Australia) Review quality rating: Good o Madah-Amiri 2019 (Norway) Review quality rating: Fair • **2 studies: No effect** o Folch 2018 (Spain) Review quality rating: Fair o Milloy 2008 (Canada) Review quality rating: Fair	Covers Potier 2014[3]
		Review of reviews: Farrell 2019[4] (Not assessed)	**Conclusion:** Significant decrease in overdose associated with drug consumption room use by people who inject drugs. Sources: • 1 review identified (systematic review) • Potier 2014[3] but see comment in Levengood 2021[2] **Review rating of evidence quality**: Level D† evidence: cross-sectional association, case series suggesting outcome, single cohort study "drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically."	Review focused on **stimulant related** harms
		Systematic review: Kennedy 2017[5] (Not assessed)	**Author conclusion:** Studies included in this review have demonstrated the contributions of SCFs to reductions in overdose-related deaths. **4 studies: Protective effect** of SCF found • Poschadel 2003 (time series, Germany) After the establishment of SCFs, there were significant reductions in drug-related deaths (all $p < 0.05$]. • NCHECR 2007 (n=1652 pre-post ecological Australia) Significant decrease from an average of 11 to 7 opioid poisoning ED presentations (35% reduction) after the SIF establishment ($p < 0.001$). • Salmon 2010 (n=20,409, pre-post ecological, Australia) After the opening of the SIF, the average monthly ambulance attendances at suspected opioid-related overdoses declined significantly in the immediate vicinity of the SIF (by 68%) compared to 61% in the rest of the state during SIF operating hours ($p = 0.002$). During the SIF operating hours, this difference was more pronounced with an 80%	

			decline in the immediate vicinity of the SIF compared to a 60% decline in the rest of the state (p <0.001). • Marshall 2011 (n=209 decedents, pre-post ecological, Canada) Fatal overdose decreased by 35.0% within 500 m from the SIF from 253.8 to 165.1 deaths per 100,000 person-years (p = 0.048) in the 2 years after the opening of the SIF vs. the 2 years prior to the SIF opening, compared to a 9.3% reduction in fatal overdose from 7.6 to 6.9 per 100,000 person-years in the rest of the city (p = 0.490). These rate changes were significantly different (p=0.049). **2 studies: No effect found** • NCHECR 2007 (n=1652 pre-post ecological Australia) No significant difference in opioid-related death rate decrease in the immediate vicinity of the SIF after the SIF was established compared to the rest of the state (p=0.877). • Milloy 2008a (n=1090 Prospective cohort Canada) No association between SIF use and rate of recent non-fatal overdose (aOR 1.01, 95% CI 0.77-1.32). **Estimate:** Mathematical simulation estimates of the number of overdose fatalities per year prevented in PWID by a supervised injection facility • Andresen & Boyd 2010 (Vancouver, Canada) **1.08** overdose deaths per year potentially averted by a Supervised Injection Facility • Hedrich 2004 (Germany) Estimate at least **10** overdose deaths per year potentially averted in Germany by supervised consumption • Milloy 2008b (Vancouver, Canada) **1.9 to 11.7** deaths per year potentially averted by the implementation of a medically supervised safer injection facility (SIF)	
		Systematic review: Tilson 2007[6] (Not assessed)	**No effect** of supervised injection facilities on prevention HIV infection among injecting drug users in high-risk countries. 1 study identified • **1 no effect:** MSIC Evaluation Committee 2003 (cross-sectional, Australia) No changes in the number of heroin overdoses in the community.	
Stimulant use	N/A	Review of reviews: Farrell 2019[4] (Not assessed)	**Effect:** Mixed or inconclusive evidence **Size of effec**t: Drug consumption rooms starting to target smoking/sniffing so could lower public stimulant use **Level of Evidence:** D (cross-sectional association, case series suggesting outcome, single cohort study) **Sources:** Rigoni 2018[7]	Review focused on **stimulant related** harms
SUD treatment utilization	N/A	Systematic review: Levengood 2021[2] (Not assessed)	**Conclusion**: **Significant improvements** in access to addiction treatment programs associated with supervised injection facilities in the included studies 7 studies identified on the association of supervised injection facilities and access to addiction treatment programs **6 studies: Positive effect** of SIF on SUD treatment utilization found	Covers Potier 2014[3] & Kennedy 2017[5]

			• Lloyd-Smith 2008, Lloyd-Smith 2009, Lloyd-Smith 2010 (Canada) Review quality rating: Fair • DeBeck 2011 (Canada) Review quality rating: Fair • Kimber 2008 (Australia) Review quality rating: Fair • Wood 2006, Wood 2007 (Canada) Review quality rating: Good • Folch 2018 (Spain) Review quality rating: Fair • Gaddis 2017 (Canada) Review quality rating: Fair **1 study: No effect found** • Milloy 2010 (Canada) Review quality rating: Fair	
		Systematic review: Kennedy 2017[5] (Not assessed)	**Conclusion**: "Several studies demonstrate the role of SCFs in facilitating entry into addiction treatment programmes and subsequent injection cessation and/or reduced injecting at SCFs. Thus, these facilities appear to support rather than undermine the goals of addiction treatment." "Consistent evidence demonstrates that SCFs facilitate uptake of addiction treatment" **3 studies: Positive effect** found of SIF on entry into SUD treatment • Wood 2006, (n=1031 prospective cohort Canada) regular SIF use (AHR = 1.72; 95% CI 1.25 2.38) and contact with the SIF addictions counsellor (AHR = 1.98; 95% CI 1.26 3.10) were associated with more rapid time to entry into a detoxification program • Wood 2007 (n=1031 prospective cohort Canada) Significant increase in uptake of detoxification services in the year after vs. the year before the SIF opened (aOR = 1.32, 95% CI 1.11-1.58). • DeBeck 2011 (n=1090 prospective cohort Canada) Regular SIF use (AHR = 1.33; 95% CI 1.04 1.72) and having contact with the addiction counsellor within the SIF (AHR = 1.54; 95% CI 1.13 2.08) were independently and positively associated with self-reported initiation of addiction treatment. **1 study: No effect** found • Kimber 2008 (n=3715 prospective cohort Australia) Frequent SIF use was positively associated with drug treatment referral (aHR = 1.6, 95% CI 1.2-2.2) but was not significantly associated with drug treatment referral uptake.	
		Systematic review: Tilson 2007[6] (Not assessed)	**Estimate:** 3 studies on supervised injection facilities in high-risk countries identified • Tyndall 2006 (cohort, Canada) In a 12-month period, the SIF made 2,171 referrals—37 percent to addiction counseling. • Wood 2006b (cohort, Canada) Regular (at least weekly) SIF use was associated with faster entry into a detoxification program (relative hazards=1.72 [1.25, 2.38]). • MSIC Evaluation Committee 2003 (cross-sectional, Australia) The MSIC made referrals for drug treatment.	
Other treatment utilization	N/A	Systematic review: Kennedy 2017[5]	**Conclusion**: Studies included in this review have demonstrated the contributions of SCFs to reductions in emergency department presentations and ambulance attendances.	

		(Not assessed)	Consistent evidence demonstrates that SCFs facilitate uptake of other health service. SCFs facilitate critical early medical intervention for the treatment of complex conditions such as cutaneous injection-related infections (CIRI). **4 studies: Positive effect** in all studies identified (2 prospective cohort, 2 cross-sectional): • Zurhold 2003 (n=616 cross-section Germany) Frequent SCF users were more likely to use counselling services (46% vs 35% vs 25%; p < 0.01) and medical services (37% vs 29% vs 17%; p <0.01) compared to occasional or rare visitors. • Lloyd-Smith 2010 (n=1083 prospective cohort Canada) Referral to hospital by SIF nurses was associated with increased likelihood of hospitalization for CIRI (aHR = 5.38, 95% CI 3.39-8.55) and independently associated with shorter duration of hospital stay (4 days [IQR 2 7] vs. 12 days [IQR 5 33]). • Lloyd-Smith 2012 (n=1083 prospective cohort Canada) Referral to hospital by SIF nurses was independently and positively associated with ED use for CIRI among females (AOR = 4.48; 95% CI 2.76 7.30) and males (AOR = 2.97; 95% CI 1.93 4.57). • Toth 2016 (n=154 cross-section Denmark) Those advised to seek medical help by staff for a medical condition were more likely to receive treatment for the condition than who were not advised to seek treatment for a condition (51.3 vs. 25.7%, p = 0.003).	
HIV infection transmission	N/A	Review of reviews: Palmateer 2022[8] (Not assessed)	**Evidence statement**: **Insufficient evidence** to either support or discount the effectiveness of Drug consumption rooms (DCRs) in the prevention of HIV transmission among PWID. "Based on no reviews, and only two weaker primary studies with mixed results" (p. 18) No reviews identified 2 studies identified (2 cross-sectional) n=1321 (range 510-811) • **1 positive**: Kennedy et al., 2019 (cross-sectional, weaker design) • **1 equivocal:** Folch et al., 2018 (cross-sectional weaker design)	
		Review of reviews: Farrell 2019[4] (Not assessed)	**Evidence statement**: **Unclear evidence** of effect of drug consumption room use on HIV incidence among people who inject drugs. 1 systematic review identified: • MacArthur [9] (review of reviews) **Review rating of evidence quality**: Grade D† evidence: cross-sectional association, case series suggesting outcome, single cohort study. "Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically."	Review focused on **stimulant related** harms
		Systematic review: Kennedy 2017[5] (Not assessed)	**Estimate:** Mathematical simulation estimates of the number of HIV infections prevented per year in PWID by a supervised injection facility • Pinkerton 2011 (Vancouver, Canada): **5.6** (90% CI 4.0 7.6) • Andresen & Jozaghi 2012 (Vancouver, Canada): **22** • Andresen & Boyd 2010 (Vancouver, Canada): **35**	

			• Pinkerton 2010 (Vancouver, Canada): **83.5** • Bayoumi & Zaric 2008 (Vancouver, Canada): **1191** over 10 years	
		Review of reviews: MacArthur 2014[9] (Not assessed)	**Evidence statement**: **Insufficient evidence** to either support or discount the effectiveness of supervised injection facilities in preventing HIV in people who inject drugs 4 reviews identified (1 core, 1 supplementary): • Tilson [6] (systematic review) No evidence statement made 1 study identified in core and supplementary reviews: • **1 equivocal**: MSIC Evaluation Committee 2003 (cross-sectional, Australia)	
		Systematic review: Tilson 2007[6] (Not assessed)	**Evidence statement: Insufficient evidence** for drawing conclusions on the effectiveness of supervised injecting facilities in reducing drug-related HIV risks among IDUs. 1 study identified: • **1 equivocal:** MSIC Evaluation Committee 2003 (cross-sectional, Australia) No increase in risk of blood-borne virus transmission	
Injection risk behaviors	N/A	Review of reviews: Palmateer 2022[8] (Not assessed)	**Evidence statement**: **Tentative evidence** to support the effectiveness of Drug consumption rooms (DCRs) n the prevention of IRB among PWID. "Only one supplementary review was identified - it included five weaker primary studies with positive results, and one cohort study with an equivocal result. Similarly, only one weaker primary study was identified, although its result was also positive. Thus, based on 'less than consistent evidence from multiple or more robust studies within one supplementary reviews' we conclude that there is insufficient evidence." (p. 18) 1 supplementary review identified: • Kennedy et al., 2017: 6 studies (1 COH, 5 CS). n=2192 (range 41-760). o 4 studies syringe sharing: 3 **positive** (3 CS); 1 **equivocal** (1 COH) o 2 studies other risk behaviors: 2 **positive** (2 CS) 1 study identified: • **Positive** effect: Folch et al 2018 (CS, n=510, weaker design)	COH=cohort CS=cross-sectional SCS=serial cross-sectional
		Systematic review: Levengood 2021[2] (Not assessed)	**Conclusion**: **Significant improvements** in injection behaviors associated with supervised injection facilities in the included studies. 7 studies of supervised injection facilities identified **5 studies: Positive findings:** Significant improvements in injection risk behaviors • Folch 2018 (cross-sectional, Spain) • Kerr 2005 (cross-sectional, Canada) Review quality rating: Fair • Bravo 2009 (cross-sectional, Spain) Review quality rating: Fair • Wood 2005 (cohort, Canada) Review quality rating: Fair • Stoltz 2007 (cohort, Canada) Review quality rating: Good **2 studies: No effect found** • Lloyd-Smith 2008 (cohort, Canada) Review quality rating: Fair • Kerr 2006 (Pre-post, Canada) Review quality rating: Fair	Covers Potier 2014[3]

		Review of reviews: Farrell 2019[4] (Not assessed)	**Positive effect:** Significant decrease in injecting risk behaviors associated with drug consumption room use by people who inject drugs 1 review identified (non-systematic meta-analysis) • Milloy 2009 (n=1262, RR=0.31 [0.17, 0.55]) combined 3 cohort studies: Kerr 2005; Wood 2005; Bravo 2009 **Review rating of evidence quality**: Grade C† evidence: high quality systematic reviews with some inconsistent conclusions from authors; or multiple consistent ecological studies, or cohort studies) "drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically."	Review focused on **stimulant related** harms
		Systematic review: Kennedy 2017[5] (Not assessed)	**3 studies: Positive effect** (inverse association between SCF use and syringe sharing) • Kerr 2005 (n=431 cross-section of prospective cohort, Canada) SIF use was associated with reduced syringe sharing (AOR = 0.30; 95% CI 0.11 0.82). • Wood 2005 (n=582 cross-section of prospective cohort, Canada) exclusive SIF use was associated with decreased odds of syringe borrowing among HIV-negative participants (OR 0.14, 95% CI 0.00-0.78) but was not significantly associated with syringe lending among HIV-positive participants (OR 0.94, 95% CI 0.00-7.90). • Bravo 2009 (n=249 cross-section Spain) SIF use associated with not borrowing used syringes (aOR 3.3, 95% CI 1.4-7.7), but not significantly associated with not sharing injection equipment (aOR 1.1, 95% CI 0.5-2.2). **1 study: No relationship found** • Scherbaum 2010 (n=129 prospective cohort Germany) Compared to baseline, at 1 month follow-up of first use of the SIF, the proportion of participants who reported use of non-sterile equipment and equipment sharing remained relatively stable at approximately 50 and 20%, respectively (all p > 0.30). Other Injection risk behaviors • Kinnard 2014 (n=41 Denmark) 75.6% reported reductions in injection risk behaviours after SIF opening (63.4% less rushed injecting; 56.1% fewer outdoor injections; 53.7% stopped syringe sharing; 43.9% cleaned injection sites more often). • Stoltz 2007 (n=760 cross-sectional Canada) consistent SIF use was positively associated with a change in each injection behaviour: reuse syringes less often (AOR = 2.04; 95% CI 1.38 3.01), less rushed during injection (AOR = 2.79; 95% CI 2.03 3.85), less injecting outdoors (AOR = 2.70; 95% CI 1.93 3.87), using clean water for injecting (AOR = 2.99; 95% CI 2.13 4.18), cooking or filtering drugs prior to injecting (AOR = 2.76; 95% CI 1.84 4.15), tying off prior to injection (AOR = 2.63; 95% CI 1.58 4.37), safer disposal of syringes (AOR = 2.13; 95% CI1.47 3.09), easier finding of a vein (AOR = 2.66; 95% CI 1.83 3.86) and injecting in a clean place (AOR = 2.85; 95% CI 2.09 3.87).	

		Review of reviews: MacArthur 2014[9] (Not assessed)	**Evidence statement: Tentative evidence** to support the effectiveness of supervised injection facilities in reducing injection risk behaviors in PWID 7 reviews identified (1 core, 6 supplementary): • Tilson 2007[6] (systematic review) Concluded evidence, while encouraging, is insufficient 7 studies identified in core and supplementary reviews: • 4 studies **positive** association found (2 longitudinal, 2 cross-sectional) o Kerr 2005 (cross-sectional, Canada); Nejedly 1996, Reyes 2013, Ronco 1996 (cross-sectional, Switzerland); Stoltz 2007 (cohort Canada); Wood 2005 (cohort, Canada) • 3 studies **no association** found (3 cross-sectional) o MSIC Evaluation Committee 2003 (cross-sectional Australia); Benninghoff 2002 (cross-sectional); Benninghoff 2003 (cross-sectional) • 6 further studies document that clients' report of positive changes to their injecting practices can be attributed to SIF	
		Systematic review: Tilson 2007[6] (Not assessed)	**Evidence statement**: **Insufficient evidence** for drawing conclusions on the effectiveness of supervised injecting facilities in reducing drug-related HIV risks among IDUs. 2 studies identified: • **1 positive:** Kerr 2005 (cross-sectional, Canada) Association between attendance and reduction in syringe sharing (adjusted OR 0.30, 95% CI 0.11–0.82, p=0.02). • **1 equivocal:** MSIC Evaluation Committee 2003 (cross-sectional, Australia) No sig diff in syringe sharing between SIF clients and non-clients	
Important Outcomes				
Hepatitis C infection transmission	N/A	Review of reviews: Palmateer 2022[8] (Not assessed)	**Evidence statement**: I**nsufficient evidence** to either support or discount the effectiveness of drug consumption rooms (DCRs) in the prevention of HCV transmission among PWID. "Based on no reviews, and only two weaker primary studies with equivocal results, we conclude that there is insufficient evidence." (p. 18) No reviews identified 2 studies identified (2 cross-sectional) n=1321, range 510-811 • **2 equivocal** (2 cross-sectional): Folch et al., 2018 (cross-sectional, weaker design); Kennedy et al., 2019 (cross-sectional, weaker design)	
		Review of reviews: Farrell 2019[4] (Not assessed)	**Evidence statement**: **Unclear evidence** of effect of drug consumption room use on HCV incidence among people who inject drugs 1 review identified: • MacArthur 2014[9] (review of reviews) **Review rating of evidence quality**: Grade D† evidence: cross-sectional association, case series suggesting outcome, single cohort stud) "†Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically."	Review focused on **stimulant related** harms

		Systematic review: Kennedy 2017[5] (Not assessed)	**Estimate:** Mathematical simulation estimates of the number of incident HCV infection cases prevented by a supervised consumption facility • Jozaghi and Vancouver Area Network of Drug Users 2014: **57** per year in people who smoke crack cocaine • Bayoumi & Zaric 2008: **54** over 10 years in PWID	
		Review of reviews: MacArthur 2014[9] (Not assessed)	**Evidence statement**: **Insufficient evidence** to either support or discount the effectiveness of supervised injection facilities in preventing HCV in people who inject drugs 3 reviews identified (1 core, 2 supplementary): • Tilson [6] (systematic review) No evidence statement made 1 study identified in core and supplementary reviews: • **1 equivocal:** MSIC Evaluation Committee 2003 (cross-sectional, Australia)	
		Systematic review: Tilson 2007[6] (Not assessed)	**No effect**: No increase in risk of blood-borne virus transmission associated with the use of Supervised Injection Facilities by injecting drug users in high-risk countries Based on 1 study (cross-sectional) • **1 equivocal**: MSIC Evaluation Committee 2003 (cross-sectional, Australia)	
Injury/morbidity risks associated with crack smoking	N/A	Systematic review: Kennedy 2017[5] (Not assessed)	2 studies (prospective cohort)**: No effect** of SIF on risk of infection found • Lloyd-Smith 2008 (n=1065 prospective cohort Canada) No association of SIF use and risk of developing cutaneous injection-related infections (aOR 0.58, 95% CI 0.29-1.19) • Scherbaum 2010 (n=129 prospective cohort Germany) At 1 month follow-up compared to baseline, the proportion who had injection-related abscesses was similar (8.5 vs 4.2%, p>0.30).	
		Systematic review: Fischer 2015[10] (Not assessed)	No rigorous evaluations of impacts of Drug Consumption Facility programs targeting crack and other drug inhalers on harm reduction outcomes found.	
Acceptability	N/A	Systematic review: Kennedy 2017[5] (Not assessed)	1 study identified • Thein 2005 (n=515 & 540 residents, cross-sectional series, Australia) 17 months after vs. 7 months before establishment of SIF: The level of support for the SIF significantly increased in the neighborhood of established SIF (68 to 78%, $p < 0.001$) among residents. There was an increase in the proportion of residents who agreed that SIFs reduce risk of HIV/ HCV (87 to 92%, $p = 0.0004$) and reduce discarded syringes (80 to 82%, $p = 0.01$). There was an increase in the proportion of residents who disagreed that SIFS encourage illicit drug injection (62 to 73%, $p < 0.001$).	
		Systematic review: Fischer 2015[10] (Not assessed)	**Estimate:** Willingness to use Drug Consumption Facility services if offered ranged from 28% to 71% of street-involved crack and other drug inhalers 4 studies identified • Bayoumi 2012 (Canada); Collins 2005 (Canada); DeBeck 2011 (Canada); Shannon 2006 (Canada)	

[i]: The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Limitations
Harocopos 2022[11]	USA	Overdose Prevention Center		Public drug use decreased	2 months of data
				Look for some non-publicly recognized in US sites	

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[12]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE • Know local and refer individuals to local resources such as Syringe services programs (SSPs), overdose prevention sites (OPS), and local harm reduction agencies. Overdose Prevention Sites • Evidence supports that OPSs reduce the harm of substances use by providing sterile drug equipment, and reduce opioid overdose fatalities.[74,76] In addition, weekly use of an OPS and any contact with the facility's counselors were independently associated with more rapid entry into a detoxification program.[77]	
Rigoni 2018[7]	Speed Limits: Harm Reduction for People Who use Stimulants Supervised inhalation rooms (SIRs) • "consider the potential role of SIRs in reducing drug-related harm" (Rigoni 2018, p. 19) • "The rationale for [supervised inhalation rooms] SIRs may be less obvious than that for SIFs, but is no less important." (Rigoni 2018, p. 19)	

	• "It therefore seems reasonable to hypothesize that co-existence of SIFs and SIRs could promote transitions from injection to non-injection, thereby reducing the risk of blood-borne infections in the community." (Rigoni 2018, p. 19)	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Overdose prevention sites are effective at reducing the incidence of overdose and overdose morbidity and mortality. Impact varies depending on SCS use frequency and site. Small impact on infection reduction. Moderate to large impact on increasing entrance into SUD treatment. Moderate reduction in injection risk behaviors. Public drug use decreased.		☐ None ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
None	No expected downsides from using the facility.	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know

Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Depends. High for overdose-related outcomes. Low for hepatitis, low-moderate for IDU, public consumption moderate, treatment utilization seems high.	Almost all of the currently published research is non-US based, although the recent opening of a few sites should increase this. For treatment utilization data, would like to see follow-up rates.	☐ No evidence ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Few publicly recognized overdose prevention sites in the US currently but anticipated that this will become more widely spread. Feasible if available. Also requires clinicians to educate themselves about how safe consumption sites work, potential practical and legal consequences for patients.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

Conclusion

Justification

Overdose prevention sites are effective at reducing the incidence of overdose and overdose morbidity and mortality. Impact varies depending on SCS use frequency and site.

Subgroup Considerations

None noted

Implementation Considerations

Few publicly recognized overdose prevention sites in the US exist currently, but it is anticipated that this will become more widely spread.

Also requires clinicians to educate themselves about how safe consumption sites work, potential practical and legal consequences for patients

References

1. Stone K, Shirley-Beavan S. *The Global State of Harm Reduction 2018*. Harm Reduction International; 2018. Accessed November 3, 2022. https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf
2. Levengood TW, Yoon GH, Davoust MJ, et al. Supervised Injection Facilities as Harm Reduction: A Systematic Review. *Am J Prev Med*. 2021;61(5):738-749. doi:10.1016/j.amepre.2021.04.017
3. Potier C, Laprévote V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: What has been demonstrated? A systematic literature review. *Drug Alcohol Depend*. 2014;145:48-68. doi:10.1016/j.drugalcdep.2014.10.012
4. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet Lond Engl*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
5. Kennedy MC, Karamouzian M, Kerr T. Public Health and Public Order Outcomes Associated with Supervised Drug Consumption Facilities: a Systematic Review. *Curr HIV/AIDS Rep*. 2017;14(5):161-183. doi:10.1007/s11904-017-0363-y
6. Tilson H, Aramrattana A, Bozzette S, et al. *Preventing HIV Infection Among Injecting Drug Users in High-Risk Countries: An Assessment of the Evidence*. Institute of Medicine; 2007. doi:10.17226/11731
7. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
8. Palmateer N, Hamill V, Bergenstrom A, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020). *Int J Drug Policy*. 2022;109:103872. doi:10.1016/j.drugpo.2022.103872

9. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *Int J Drug Policy*. 2014;25(1):34-52. doi:10.1016/j.drugpo.2013.07.001
10. Fischer B, Blanken P, Da Silveira D, et al. Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: a comprehensive narrative overview of English-language studies. *Int J Drug Policy*. 2015;26(4):352-363. doi:10/f66rht
11. Harocopos A, Gibson BE, Saha N, et al. First 2 Months of Operation at First Publicly Recognized Overdose Prevention Centers in US. *JAMA Netw Open*. 2022;5(7):e2222149. doi:10.1001/jamanetworkopen.2022.22149
12. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 63. Prevention Routine STI Testing

Recommendation: For patients who engage in risky sexual behaviors, clinicians should:

a. offer testing for STIs at least every 3 to 6 months or more frequently depending on the individual patient's risk as per CDC and USPSTF Guidelines.

i. consider providing information about local STI testing services where patients can obtain free or low-cost testing

Clinical Question Summary

Clinical Question	How often should STI testing be conducted in patients with StUD and other StUD-related risk factors?
Population	Patients who use stimulants and engage in risky sexual behaviors
Intervention	HCV testing + informing of serostatus
Comparison	TAU
Main Outcomes	Early detection of STI
Setting	Clinical settings
Background & Definitions	Notes: • See EDU sex
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
General	N/A	Systematic Review: Timmerman 2018[1]	Timmerman K, Weekes M, Traversy G, et al. Evidence for optimal HIV screening and testing intervals in HIV-negative individuals from various risk groups: A systematic review. *Can Commun Dis Rep*. 2018;44(12):337-347. https://doi.org/10.14745/ccdr.v44i12a05	
General	N/A	Systematic Review: Tiwari 2020[2]	Tiwari R, Wang J, Han H, et al. Sexual behaviour change following HIV testing services: A systematic review and meta-analysis. *J Int AIDS Soc*. 2020;23(11): e25635. https://doi.org/10.1002/jia2.25635	

Stimulant use	N/A	Review of reviews: Farrell 2019[3] (Supplementary)	HIV testing + informing of serostatus • No evidence could be located of the impact of this intervention upon the outcome HCV testing + informing of serostatus • No effect • Source: Spellman 2015 • Level of Evidence: C* (High quality systematic reviews with some inconsistent conclusions from authors; OR multiple consistent ecological studies, or cohort studies. *Evidence drawn from people who inject drugs and not specific to stimulant users, however we have no reason to believe this intervention would operate differently among stimulant users specifically.)	Review focused on **stimulant related** harms.

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Existing Guidelines

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):192. doi:10.15585/mmwr.rr7004a1

Evidence to Decision (EtD) Table:

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No specific evidence on referring or providing STI testing in stimulant users. Risky sexual behaviors are more prevalent in stimulant users. Reduced STI incidence, Any and earlier identification of STI and treatment. Treatment also reduces transmission.		☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
If onsite testing, high If referring, also requires linkage and follow-through, so downgrade to moderate		☐ Clinical judgment (no evidence) ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies

***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

While no specific evidence was found on referring or providing STI testing to people who use stimulants, it is known that risky sexual behaviors are more prevalent in this population, and earlier identification of STIs is beneficial and reduces transmission

Subgroup Considerations

More frequent testing may be indicated depending on the individual patient's risk

Implementation Considerations

Implementation requires clinician knowledge of local resources

References

1. Timmerman K, Weekes M, Traversy G, et al. Evidence for optimal HIV screening and testing intervals in HIV-negative individuals from various risk groups: A systematic review. *Can Commun Dis Rep*. 2018;44(12):337-347. https://doi.org/10.14745/ccdr.v44i12a05
2. Tiwari R, Wang J, Han H, et al. Sexual behaviour change following HIV testing services: A systematic review and meta-analysis. *J Int AIDS Soc.* 2020;23(11): e25635. https://doi.org/10.1002/jia2.25635
3. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5

Table 64. Education Injection Drug Use

Recommendation: For patients who inject stimulants, clinicians should:

a. provide or refer for harm reduction education on safer injection practices and include information specific to the patients' stimulant(s) and preparation(s) of choice (eg, safer acid pairings for crack cocaine injection).

Clinical Question Summary Table

Clinical Question	What educational interventions are effective for reducing harms related to injection drug use?
Population	People who inject drugs (PWID)
Intervention	Information, education and counseling
Comparison	No education
Main Outcomes	Health outcomes
Setting	Clinical settings
Background & Definitions	Background information on the question, more detailed description of the interventions Notes: Injection drug use prevalence • "Among adults reporting past-year MA use between 2015 and 2018, 22.3 percent injected MA (C. M. Jones et al., 2020)." (SAMHSA Tip 33, 2021, p151)[1] Are PWI Stimulants at greater risk of infection than PWI Other Drugs? • "The potential negative health consequences associated with the use of stimulant drugs is partly substance-dependent and partly related to specific routes of administration." (Rigoni 2018, p18)[2] • "In a meta-analysis of global HIV risk among PWID (including in North America), the risk of HIV incidence was 3.6 times higher for people injecting cocaine and 3.0 times higher for people injecting amphetamine-type stimulants, compared with the risk for people who had not injected the drugs in the previous 6 months (Tavitian-Exley et al., 2015)." (SAMHSA Tip 33, 2021, p151)[1] • "People who inject stimulants may be at elevated risk for HIV acquisition compared with individuals who inject other substances, because of the frequency with which injection of stimulants occurs (Tavitian-Exley et al. 2015)." (SAMHSA Tip 33, 2021, p152)[1] • Risk of infection may be increased in PWID due to pattern of use. Cocaine is frequently binged, leading to more frequent injections compared to opioids (Foltin et al., 2015; Vosburg et al., 2010) (SAMHSA Tip 33, 2021, p151)[1] Are PWID are at greater risk of infection than… the general public? Other substance users? • "Data from CDC suggest that PWID are about 16 times more likely than people without injection drug use to develop invasive methicillin-resistant Staphylococcus aureus (staph) infections (Jackson et al., 2018)" (SAMHSA Tip 33, 2021, p151)[1] • "People engaging in injection drug use are at increased risk of infectious endocarditis, which accounts for 5 to 25 percent of hospitalizations for acute infection among people who inject drugs (Visconti et al., 2019)." (SAMHSA Tip 33, 2021, p57)[1]

	• "Another emerging medical issue related to injection drug use CDC has identified is infective endocarditis (an infection in the heart; CDC, n.d.-e). Injection drug use is the main cause of infective endocarditis. Anywhere from 5 to 10 percent of total deaths among PWID are due to this condition (Ji et al., 2012), which has an inpatient mortality rate of about 5 to 8 percent." (SAMHSA Tip 33, 2021, p151)[1] • The primary mode of HCV transmission is injection drug use (SAMHSA Tip 33, 2021)[1] • "Increased HIV and hepatitis B and C transmission are likely consequences of stimulant use, particularly in individuals who inject intravenously and share equipment. HIV and other blood-borne pathogens may spread through communities of people injecting drugs via shared injection equipment or unprotected sex. People who injected drugs accounted for 9 percent of all new cases of HIV diagnosed in 2017 (Centers for Disease Control and Prevention, 2021b)." (SAMHSA Tip 33, 2021, p57) [1] • "A growing body of research has examined high-risk injection practices that contribute to bacterial infections. Findings, including from our own research, generally indicate that frequent injection (especially of black tar heroin, cocaine and speedballs), subcutaneous or intramuscular injection, lack of skin cleaning at the injection site, and reusing or sharing injection equipment contribute most significantly to these infections (Binswanger et al., 2000; Phillips & Stein, 2010; Murphy et al., 2001; Vlahov, Sullivan, Astemborski, & Nelson, 1992)." (Phillips 2013, p2)[3] Are PWID are at greater risk of VASCULAR & NERVE DAMAGE • **All of the problems associated with use of drugs by injection** on peripheral vascular and nerve damage **are exacerbated by the chemical properties of stimulants.** (SAMHSA Tip 33, 2021, p61)[1] Are PWID are at greater risk of OVERDOSE • Methamphetamine Use, Methamphetamine Use Disorder, and Associated Overdose Deaths Among US Adults (Han 2021)[4] Other • "concurrent heroin and methamphetamine injection is associated with injection frequency, re-using syringes and sharing syringes (Al-Tayyib et al 2017)" (Imtiaz 2020, p1189)[5] • STI/HIV prevention programs for PWID should emphasize **safer sex** as well as safer injection practices. injection drug use is independently associated with over twice the prevalence of STIs, and elevated risk is more likely attributed to higher rates of sex with infected partners rather than multiple partners or inconsistent condom use. (Khan 2013)[6] • Among young adults in the US, non-injection **crack/cocaine use** is associated with moderate elevations in the prevalence of biologically confirmed STIs (adjusted prevalence ratio (APR): 1.63, 95% CI: 1.10–2.42) even after adjusting for age at first sex, socio-demographic factors (particularly race), and alcohol and other drug use. (Khan 2013)[6] The association did not materially change when further adjusting for indicators of multiple partnerships, inconsistent condom use, and sex with an STI-infected partner in the past year (APR: 1.69, 95% CI: 1.13–2.52), suggesting these risk indicators did not explain the moderate elevations in STI levels observed. For injection drug users, however, the elevated prevalence of biologically confirmed STIs adjusted for age at first sex, socio-demographic factors, alcohol and other drug use (APR: 2.66, 95% CI: 1.18–5.99) was weakened after adjusting for multiple partnership and inconsistent condom use variables (APR: 2.55, 95% CI: 1.03–5.80) and was weakened by more than 20% and no longer significant after the inclusion of sex with an STI-infected partner (APR: 1.98, 95% CI: 0.68–4.73). "The analyses suggested that elevated risk among IDUs is more likely attributed to elevated risk of sex with infected partners than to elevated levels of multiple partnerships and inconsistent condom use." (Khan 2013, p7)[6] • Among young adults in the US, crack/cocaine use is associated with moderate elevations in the prevalence of **STIs** (Khan 2013)[6]

	• "Grund et al. (2010) have created an overview of the relation between (injection) stimulant use and HIV and HCV (Grund et al. 2010, 194–95)." (Rigoni 2018, p18)[2] "An additional risk [of infectious diseases (eg blood-borne viruses such as HCV and HIV)] for people who inject stimulants is that they… engage more frequently in risky sexual activities **compared to people who inject heroin** (Grund et al. 2010; Folch et al. 2009)" (Rigoni 2018, p18)[2]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **IDU**: Injection drug use, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MSM**: Men who have sex with men, **N**: Number, **PWID**: People who inject drugs, **RCT**: Randomized Control Trial, **SMD**: Standard Mean Difference, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Treatment entry	N/A	Meta-analysis: Copenhaver 2006[7] (Not assessed)	37 RCTs on group or individual-level behavioral HIV prevention interventions (average 8 sessions, 70% targeting both drug- and sex-related risk) vs Control (eg brief HIV risk-reduction intervention, HIV education alone wait-list) with at least 50% of participants reporting recent injection drug use. Half (54%) of IUD participants reported injecting cocaine. Half (47%) of the studies recruited out-of-treatment participants, while the remainder were in treatment. **Behavioral HIV prevention interventions** increased entry into drug treatment compared to Control in 6 RCTs (SMD=0.11, [0.02, 0.21]; OR=0.81 [0.68–0.96]; heterogeneity I^2=41%, p=0.13). Did not list the individual studies.	Behavioral HIV risk reduction interventions among people who inject drugs* Johnson 2020[8]'s rating: PRISMA 21/27, AMSTAR 8/11
Recurrent endocarditis	N/A	Review of reviews: Puzhko 2022[9] (Not assessed)	Insufficient SR-level evidence to support effectiveness of educational sessions on skin and needle hygiene in prevention infectious endocarditis (only 1 study) • Bahji 2020 (high-quality narrative synthesis) Conclusion of SR: Tentative evidence to support effectiveness of behavioral interventions to reduce recurrent infectious endocarditis.	Interventions to prevent infections in **opioid users**
		Systematic review: Bahji 2020[10] (Not assessed)	Skin and needle hygiene educational intervention for 6 months for adults with injection drug use-related infectious endocarditis in the context of opioid use disorder compared to control group. (1 study, n=48, HR=0.80 [0.37, 1.74])	People with **opioid use disorder** Puzhko 2022[9]'s rating: AMSTAR2 = High
HIV infection	N/A	Review of reviews:	**Insufficient** evidence to either support or discount the effectiveness of information, education and counselling interventions in preventing HIV.	Interventions to prevent HIV and

		MacArthur 2014[11] (Not assessed)	Review-level evidence: • **Tilson 2007** [12] does not provide a statement of evidence • Needle et al. (2005) provides a tentative statement of evidence in support of community-based outreach 3 studies identified in reviews • All positive results (1 longitudinal cohort, 1 cross-sectional, 1 ecological)	Hepatitis C in people who inject drugs*
HCV infection	N/A	Review of reviews: MacArthur 2014[11] (Not assessed)	**Insufficient** evidence to either support or discount the effectiveness of <u>information, education and counselling interventions</u> in preventing HCV. • No review-level evidence found • 1 study identified (cross-sectional), positive result	Interventions to prevent HIV and Hepatitis C in people who inject drugs*
		Meta-analysis: Hagan 2011[13] (Not assessed)	**No significant effect** of **Behavioral interventions** on HCV incidence among PWID in 2 RCTs. No significant heterogeneity (I-squared=0%). • Garfein 2007 (RCT, n=854 USA, 6-session peer education vs control) • Stein 2009 (RCT, n=89 USA, interventionist-delivered 4-session MI vs control)	Interventions to prevent hepatitis C virus infection in people who inject drugs Puzhko 2022[9]'s rating: AMSTAR2 = Low

Any injection risk behaviors	N/A	Meta-analysis: Gilchrist 2017[14] (Not assessed)	<u>Psychosocial Interventions (Harm Reduction individual/group counseling, MI, MET, skills training, peer education/mentoring, CBT, Contingency management) vs…</u>
			Psychosocial Interventions demonstrated greater reductions in any injection risk behaviors compared to:
			• <u>Any control</u> (22 studies, n=6067, SMD= -0.29 [-0.42, -0.15], p<0.001) with significant heterogeneity (I^2=61%, p<0.001)
			• <u>Education/ information</u> (5 studies, n=1050, SMD= -0.41 [-0.79, -0.04], p=0.03) with significant heterogeneity (I^2=62%, p=0.03)
			  ○ Bertrand 2015; Go 2013; Otiashvili 2012; Tobin 2010; Tucker 2004
			• <u>HIV testing and counselling</u> (3 studies, n=1145, SMD= -0.24 [-0.44, -0.03], p=0.02; [I^2=0%, p=0.45])
			  ○ Go 2015; Latkin 2009; Robles 2004
			• <u>Lower time or intensity interventions without OST</u> (9 studies, n=3101, SMD= -0.34 [-0.56, -0.12], p=0.003) with significant heterogeneity (I^2 = 75%, p < 0.001)
			  ○ Abou-Saleh 2008; Garfein 2007 (RCT, n=854, 6-session peer education vs control); Gilbert 2010; Latka 2008; Latkin 2003; Purcell 2007; Samet 2015; Sterk 2003; Wechsberg 2012
			No difference in injection risk behaviors was found when compared with:
				Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

			• Lower time or intensity interventions with OST (2 studies, n=130, p=0.54; [I^2=0%, p=0.47])
			  o Margolin 2003; Schroeder 2006
			• Treatment as usual (3 studies, n=641, p=0.48; [I^2=26%, p=0.26])
			  o Booth 2011; Stein 2002; Stein 2005	

		Review of reviews: MacArthur 2014[11] (Not assessed)	Tentative evidence of effectiveness of **information, education and counselling** interventions in reducing injection risk behavior.
			• Review-level evidence:
			  o Medley et al. (2009) provides a tentative statement of evidence in support of peer education interventions.
			  o Herbst et al. (2007) do not provide a statement of evidence
			  o Tilson et al. (2007) provides a tentative statement of evidence in support of outreach and education
			  o Needle et al. (2005) provides a statement of evidence in support of community-based outreach
			  o Prendergast (2001) provides a tentative statement of evidence in support of IEC delivered within a drug treatment program
			  o Copenhaver et al. (2006) provides a statement of evidence in support of behavioural interventions
			• 28 studies identified in reviews:
			  o 18 positive (7 RCT, 10 longitudinal cohort, 1 cross-sectional)
			  o 10 no association (8 RCT, 2 cross-sectional)
				Interventions to prevent HIV and Hepatitis C in people who inject drugs*

		Meta-analysis: Meader 2010[16] (Not assessed)	*(1) Multi-session psychosocial interventions (to reduce injection and/or sexual risk behavior) vs Standard education*
			• **No significant difference** in injection risk behavior reduction at 3-6-month follow-up in 6 RCTs (n= 1044, p=0.77). Significant heterogeneity (I^2=69%, p=0.01).
			  o Avants 2004 (n=220 [190] PWID in MMT [46% CoUD], 12-session Psychoed vs 1-session MI + Standard care [2 hours counselling & case management per month])
			  o Baker 1993 (n=95 PWID in MMT, 6-session Psychoed vs 1-session MI vs Standard care [Advice & Booklet])
			  o Baxter 1991 (n=134 PWID in prison, 6-session Psychoed vs Control)
			  o Dushay 2001 (n=539 Puerto Rican or Black, 3-session culturally-appropriate Psychoed vs 2-session Standard education)
			  o O'Neill 1996 (n=92 [80] PWID in MMT, 6-session Psychoed vs Standard care)
			  o Sterk 2003 (n=48 out-of-treatment female African-American active IDUs, 4-session tailored HIV Motivational Psychoed vs NIDA Standard HIV Intervention) Favorable for injection frequency
				Cochrane Review of 35 RCTs on **opiates &/or cocaine misuse**
				
				Johnson 2020[8]'s rating: PRISMA 23/27, AMSTAR 10/11

			• **Multi-session Psychosocial Intervention** groups had greater a reduction in injection risk behavior at >6-month follow-up in 1 RCT (n=73, SMD= -0.81 [-1.29, -0.33], p<0.001).
			  o O'Neill 1996 (n=92 PWID in MMT, 6-session Psychoeducation vs Standard care)
			• **No significant difference** in the proportion of participants engaging in safer injection behavior at 3-6-month follow-up in 7 studies (k=13, n= 6562, p=0.48). Significant heterogeneity (I^2=59%, p<0.001).
			  o Colon 1993; Deren 1995; Kotranski 1998; Margolin 2003; NADR (k=7); Robles 2004; Siegal
			(2) Multi-session psychosocial interventions (to reduce injection and/or sexual risk behavior) vs Minimal intervention control
			• **No significant difference** in reductions in injection risk behavior in 2 RCTs (n=107, p=0.8).
			  o Sorensen 1994a (n=60 in opiate detox, 2-session Psychoeducation vs Control)
			  o Sorensen 1994b (n=50 in MMT, 3-session Psychoeducation vs Control)
			(3) Standard education vs Minimal control
			• **No significant difference** in injection risk behavior reduction at 3-6-month follow-up in 3 RCTs (n=262, p=0.64)
			  o Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet])
			  o Baker 1994 (n=200 PWID, 1-session MI vs Standard care)
			  o Tucker 2004 (n=145 PWID, 1-session MI vs Booklet)
			• **No significant difference** in proportion of participants engaging in safer injection behavior at 3-6-month follow-up in 4 studies (n=510, p=0.32)
			  o Gibson 1999a (PWID w/ OUD, 1-session Education vs Booklet)
			  o Gibson 1999b (PWID w/ OUD, 1-session Education vs Control)
			  o Mandell 1994 (Out of Tx PWID, 1-session BI vs Minimal information)
			  o Stein 2002 (PWID w/ AUD, 2-session MI vs Control)	

Injection drug use	N/A	Review of reviews: Tran 2021[17] (Not assessed)	**CBT** groups had lower odds of injection drug use at the end of treatment compared to Control groups in 2 studies of people who use ATS (n=816, OR=0.35 [0.24, 0.49], p<0.001; Certainty of evidence: Low). • Rawson 2008[18] (n=784 MaUD, **Matrix Model CBT** vs TAU) Reduced frequency of injecting MA (p<0.001), use of dirty needles (p<0.001), sharing cooker, cotton, etc. in past 30 days from baseline to discharge (p<0.01) (n=128). • Shoptaw 2008[19] (n=23 stimulant using MSM, **G-CBT** vs gay-specific social support therapy [GSST]).	Psychosocial interventions for **ATStUD*** Shoptaw 2008 citation might be incorrect or unpublished data.

		Meta-analysis: Gilchrist 2017[14] (Not assessed)	Psychosocial Interventions vs…
			Psychosocial Interventions appear to reduce frequency of injecting compared to:
			• Any control (8 studies, 2826, SMD= -0.17 [-0.35, 0.00], p=0.05) with significant heterogeneity (I^2=61%, p=0.01)
			• Education/information (1 study, n=40, SMD= -1.05 [-2.07, -0.03], p=0.04)
			  o Otiashvili 2012
			No difference in frequency of injecting was found when compared with:
			• Treatment as usual (1 study, n=423, p=0.96)
			  o Booth 2011
			• HIV testing & counselling (3 studies, n=2087, p=0.20) with significant heterogeneity (I^2=76%, p=0.01)
			  o Latkin 2009; Robles 2004; Rotheram 2010
			• Lower time or intensity interventions without OST (2 studies, n=168, p=0.20; [I^2=66%, p=0.09])
			  o Sterk 2003; Wechsberg 2012
			• Lower time or intensity interventions with OST (1 study, n=40, p=0.80)
			  o Schroeder 2006
				Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

		Meta-analysis: Copenhaver 2006[7] (Not assessed)	**Behavioral HIV prevention interventions** reduced the frequency of injection drug use compared to Control in 17 RCTs (k=30, SMD=0.08, [0.03, 0.13]) with significant heterogeneity (I^2=65%, p<0.001). • Avants 1999; Avants 2004; Baker 2001; Baker 1993; Calsyn 1992; Compton 1996; Deren 1995; Latkin 1999; Latkin 2003; Mandell 1994; Margolin 2003; NADR 1994; Robles 1993; Sorensen 1994; Stein 2002; Sterk 2003; Yancovitz 1991 The effect was stronger for interventions which: • Placed equal emphasis on both injection- and sexual-risk behaviors (k=30, β=0.626, p<0.001) • Provided interpersonal skills training specific to safer needle use (k=30, β=0.261, p<0.05) Effect was still significant up 52 weeks following intervention based on 6 studies with follow-up data. Did not list the included studies.	Behavioral HIV risk reduction interventions among people who inject drugs* k=comparisons Johnson 2020[8]'s rating: PRISMA 21/27, AMSTAR 8/11
Sharing needles/ equipment	N/A	Meta-analysis: Gilchrist 2017[14] (Not assessed)	Psychosocial Interventions vs… **Psychosocial interventions** appear to reduce frequency of sharing of needles/syringes compared to: • Any control (13 studies, n=2730, SMD= -0.43 [-0.69, -0.18], p<0.001) with significant heterogeneity (I^2=68%, p<0.001) • Education/information (3 studies, n=678, SMD= -0.52 [-1.02, -0.03], p=0.04; [I^2=0%, p=0.33]) o Bertrand 2015; Go 2013; Otiashvili 2012	Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

			• HIV testing/counselling (3 studies, n=1145, SMD= -0.24 [-0.44, -0.03], p=0.02; [I^2 =0%, p=0.45]) o Go 2015; Latkin 2009; Robles 2004 **A trend for psychosocial interventions** showing greater reductions in sharing of needles/syringes compared to: • Treatment as usual (1 study, n=109, SMD= -0.53 [-1.12, 0.07], p=0.08) o Stein 2002 • Lower time or intensity interventions without OST (4 studies, n=668, SMD=-0.56 [-1.22, 0.09], p=0.09) with significant heterogeneity (I^2=90%, p<0.001) o Gilbert 2010; Latkin 2003; Samet 2015; Sterk 2003 **No difference** in sharing of needles/syringes was found when compared with: • Lower time or intensity interventions with OST (2 studies, n=130, p=0.83; [I^2=63%, p=0.10]) o Margolin 2003; Schroeder 2006	
		Meta-analysis: Copenhaver 2006[7] (Not assessed)	**No significant difference** between Behavioral HIV prevention interventions and Control in frequency of sharing of needles/syringes (k=16 contrasts; heterogeneity I^2=38%, p=0.06). Did not list the included studies.	Behavioral HIV risk reduction interventions among people who inject drugs* Johnson 2020[8]'s rating: PRISMA 21/27, AMSTAR 8/11
Sharing other injecting paraphernalia	N/A	Meta-analysis: Gilchrist 2017[14] (Not assessed)	Psychosocial Interventions vs… **Psychosocial Interventions** reduced the frequency of sharing injecting paraphernalia other than needles/syringes compared to: • Any control (7 studies, n=2366, SMD= -0.21 [-0.42, -0.06], p<0.001; [I^2=0%, p=0.83]) • HIV testing/counselling (3 studies, n=1145, SMD= -0.17 [-0.34, 0.00], p=0.05; [I^2=0%, p=0.77]) o Go 2015; Latkin 2009; Robles 2004 • Lower time or intensity interventions without OST (3 studies, n=1002, SMD= -0.24 [-0.42, -0.06], p=0.008; [I^2 =0%, p=0.48]) o Garfein 2007 (RCT, n=854, 6-session peer education vs control); Sterk 2003; Wechsberg 2012 **No difference** in frequency of sharing other injecting paraphernalia was found when compared with: • Education/information (1 study, n=219, p=0.15) o Bertrand 2015	Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

Any sexual risk behavior	N/A	Meta-analysis: Gilchrist 2017[14] (Not assessed)	Psychosocial Interventions vs…
			A trend for Psychosocial Interventions showing greater reductions in sexual risk behaviors compared to:
			• Any control (10 studies, n=2768, SMD= -0.19 [-0.39, 0.01], p=0.07) with significant heterogeneity (I^2=58%, p=0.01)
			No difference in sexual risk behaviors was found when compared with:
			• Education/information (3 studies, n=1223, p=0.27; [I^2=34%, p=0.22])
			  ○ Tobin 2010; Tucker 2004; Zule 2009
			• HIV testing/counselling (1 study, n=174, p=0.77)
			  ○ Go 2015
			• Lower time or intensity interventions without OST (4 studies, n=1241, p=0.21) with significant heterogeneity (I^2=78%, p=0.003)
			  ○ Abou-Saleh 2008; Gilbert 2010; Purcell 2007; Wechsberg 2012
			• Lower time or intensity interventions with OST (2 studies, n=130, p=0.79 [I^2=58%, p=0.06])
			  ○ Margolin 2003
			  ○ Schroeder
				Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

Condom use	N/A	Meta-analysis: Gilchrist 2017[14] (Not assessed)	Psychosocial Interventions vs…
			Psychosocial Interventions reduced unprotected sex compared to:
			• Any control (8 studies, n=1806, SMD= -0.27 [-0.54, -0.01], p=0.04) with significant heterogeneity (I^2=68%, p=0.003)
			• Lower time or intensity interventions without OST (4 studies, n=651, SMD= -0.44 [-0.86, -0.01], p=0.04) with significant heterogeneity (I^2=79%, p=0.003)
			  ○ Gilbert 2010; Samet 2015; Sterk 2003 (n=48 out-of-treatment female African-American active IDUs, 4-session tailored HIV Negotiation Psychoed vs NIDA Standard HIV Intervention) Depended on partner type (steady, casual, paying); Wechsberg 2012
			No difference in unprotected sex was found when compared with:
			• Education/information (1 study, n=852, p=0.79)
			  ○ Zule 2009
			• HIV testing/counselling (1 study, n=174, p=0.77)
			  ○ Go 2015
			• Lower time or intensity interventions with OST (2 studies, n=130, p=0.81 [I^2=70%, p=0.07])
			  ○ Margolin 2003; Schroeder
				Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

		Meta-analysis: Copenhaver 2006[7] (Not assessed)	**Behavioral HIV prevention interventions** increased frequency of condom use relative to Control conditions across 11 RCTs (k=16, SMD=0.19, 95% CI [0.12, 0.26]) with significant heterogeneity (I^2=48%, p=0.02). • Avants 2004 (MMT, Harm Reduction group)	Behavioral HIV risk reduction interventions among

			• Calsyn 1992 (PWID, Education, Education & testing); • Deren 1995 (Standard education, Enhanced education); • Gibson 1999 (PWID, Brief counseling, Brief counseling & testing); • Latkin 2003 (Peer outreach); • Margolin 2003 (PWID w/ HIV, Manualized intervention); • Robles 1993; • Sorensen 1994 (Psychoeducation); • Stein 2002 (Needle exchange, BI); • Sterk 2003 (n=68 out-of-treatment African-American female active IDUs, 4-session tailored Motivational HIV Psychoed vs 4-session tailored Behavioral HIV Psychoed vs NIDA Standard HIV Intervention) Depended on partner type (steady, casual, paying) **Behavioral intervention** effect remained significant at follow-up based on 7 studies with follow-up data. Did not list the included studies.	people who inject drugs* Johnson 2020[8]'s rating: PRISMA 21/27, AMSTAR 8/11
		Meta-analysis: Copenhaver 2006[7] (Not assessed)	**No significant difference** between Behavioral HIV prevention interventions and Control in frequency of unprotected sex (k=15 contrasts; heterogeneity I^2=26%, p=0.17). Did not list the included studies.	Behavioral HIV risk reduction interventions among people who inject drugs*

Number of sexual partners	N/A	Meta-analysis: Gilchrist 2017[14]
		(Not assessed)
			<u>Psychosocial Interventions vs…</u>
			Psychosocial Interventions reduced the number of sexual partners compared to:
			• <u>Lower time or intensity interventions without OST</u> (1 study, n=48, SMD= 3.24 [2.36, 4.12], p<0.001)
			  ○ Sterk 2003 (n=48 out-of-treatment female African-American active IDUs, 4-session tailored HIV Negotiation Psychoed vs NIDA Standard HIV Intervention)
			No difference in number of sexual partners was found when compared with:
			• <u>Education/information</u> (1 study, n=227, p=0.89)
			  ○ Tobin 2010 (n=227 PWID, 7- session Peer educator intervention vs 5-session Group information)
			• <u>Any comparator</u> (2 studies, n=275, p=0.17) with significant heterogeneity (I^2=98%, p<0.001)
			  ○ Sterk 2003 (n=48 out-of-treatment female African-American active IDUs, 4-session tailored HIV Negotiation Psychoed vs NIDA Standard HIV Intervention)
			  ○ Tobin 2010 (n=227 PWID, 7- session Peer educator intervention vs 5-session Group information)
				Psychosocial interventions to reduce drug and sexual blood borne virus risk behaviors among people who inject drugs*

Injection and sexual risk behavior combined	N/A	Meta-analysis: Meader 2010[16] (Not assessed)	<u>Multi-session psychosocial interventions designed to reduce injection and/or sexual risk behavior vs Standard education</u> **Trend towards Multi-session Psychosocial Interventions** having greater reductions in sexual and injection risk behaviors in 11 RCTs (n=1427, SMD= -0.17 [-0.37, 0.03], p=0.09) with significant heterogeneity ([I^2=62%, p<0.001). • **Multi-session Psychosocial Intervention** effect was significant for participants in formal drug treatment (8 RCTs, n=706, SMD=-0.28 [-0.44, -0.12], p<0.001; [I2=10%, p=0.36]). o Avants 2004 (n=220 PWID in MMT [46% CoUD], 12-session Psychoeducation vs 1-session MI + Standard care [2 hours counselling and case management per month]) o Baker 1993 (n=95 PWID in MMT, 6-session Psychoeducation vs 1-session MI vs Standard care [Advice & Booklet]) o Eldridge 1997 (n=104 court-mandated IPT, 6-session Psychoeducation vs 2-session Standard education) o Harris 1998 (n=204 women in MMT, 16-session women-focused Psychoeducation vs Standard care [MMT]) o O'Neill 1996 (n=92 PWID in MMT, 6-session Psychoeducation vs Standard care) o Schilling 1991 (n=91 women in MMT, 5-session Psychoeducation vs Standard education) o Sorensen 1994a (n=60 in opiate detox, 2-session Psychoeducation vs Control) o Sorensen 1994b (n=50 in MMT, 3-session Psychoeducation vs Control) • **No significant effect** for participants not in formal treatment (3 RCTs, n=721, SMD=0.11 [-0.32, 0.54], p=0.61) with significant heterogeneity (I2=76%, p=0.02). o Baxter 1991 (n=134 PWID in prison, 6-session Psychoeducation vs Control) o Dushay 2001 (n=539 Puerto Rican or Black, 3-session culturally-appropriate Psychoeducation vs 2-session Standard education) o Sterk 2003 (n=48 out-of-treatment female African-American active IDUs, 4-session tailored HIV Motivational Psychoed vs NIDA Standard HIV Intervention) **Multi-session Psychosocial Interventions** had more participants engaging in safer injection and sexual risk behavior in 11 RCTs (k=17, n= 5763, RR= 1.12 [1.04, 1.2], p<0.001). Significant heterogeneity (I^2=64%, p=0.01). • **Multi-session Psychosocial Intervention** effect was significant for participants in formal drug treatment (3 RCTs, 341 participants, RR= 1.42 [1.14, 1.77], p<0.001; [I2=0%, p=0.45]))	Cochrane Review of 35 RCTs of **opiate &/or cocaine misuse** Johnson 2020[8]'s rating: PRISMA 23/27, AMSTAR 10/11ef

			○ Eldridge 1997 (n=104 justice-involved tx, 6-session Psychoeducation vs 2-session Standard education) ○ Malow 1994 (n=152 Crack CoUD, 3-session Psychoeducation vs Control) ○ Margolin 2003 (n=90 MMT, 6-session Psychoeducation vs Group counseling) • **Multi-session Psychosocial Intervention** effect was significant for participants not in formal drug treatment (7 RCTs, k=13, 5277 participants, RR= 1.10 [1.02, 1.18], p=0.01; [I2=67%, p<0.001]). ○ Colon 1993 (n=1866, 3-session Psychoeducation vs Control) ○ Deren 1995 (n=1770 PWID or partner, 3-session Psychoeducation vs 1-session Standard education) ○ El-Bassel 1995 (n=145 incarcerated women, 16-session psychoeducation vs 2-session Standard education) ○ Kotranski 1998 (n=417 PWID, 3-session Psychoeducation vs 2-session Standard education) ○ NADR (k=7) ○ Robles 2004 (n=557 PWID, 6-session Psychoeducation vs 2-session Standard education) ○ Siegal 1995 (n=381 needle exchange, 4-session Psychoeducation vs 1-session Enhanced standard care) ○ Wechsberg 2004 (n=60 out-of-tx Black women who use crack, 4-session woman-focused Psychoeducation vs Waitlist)	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

*Evidence drawn from people who inject drugs and not specific to stimulant users, however we have no reason to believe this intervention would operate differently among stimulant users specifically.

NIDA Standard HIV Intervention for drug users: Coyle S. The NIDA HIV counseling and education intervention model: intervention manual (NIH Pub. No. 93-3508). Rockville: National Institute on Drug Abuse; 1993.

Characteristics of Individual Studies Table

Study	Design	Intervention	Participants	Outcomes	Comments
Rawson 2008[18]	RCT	Matrix Model CBT vs TAU	n=784 MaUD	Reduced frequency of injecting MA (p<0.001), use of dirty needles (p<0.001), sharing cooker, cotton, etc. in past 30 days from baseline to discharge (p<0.01) (n=128).	In Tran 2021[26]

	Outpatient SUD treatment				
Smout 2010[28]	Longitudinal cohort 3-month follow-up Australia Community	**Psychostimulant Check-Up**: Single-session brief intervention for stimulant users	N=80 adults (39% female) who used psychostimulants (**98% injected MA as usual route of administration**) in the previous month recruited though community advertisements and fliers. A majority of participants (55) were in the 'action' stage of readiness to change at baseline.	Follow-up rate 62% **Injection drug use** (self-report): Significant reduction in self-reported injection as the usual route of administration at follow up (n=11, 78% vs 55%, p=0.004). **Other outcomes**: MA use, MA-related negative consequences, Readiness to change, Treatment engagement, Patient satisfaction	Also see EtDT Prev SBI, EtDt Prev Refer to Tx
Stein 2009[29]	RCT 6 months Up to 24-mo follow-up USA Community	**(1) MI:** Four-session motivational intervention (30-45 mins each) to reduce HCV risk behaviors adapted from the Brief Alcohol Intervention in Needle Exchangers (BRAINE) manual + Referral handout (n=140) **(2) Control:** Referral handout (n=137)	N=277 adult HCV negative out-of-treatment heroin and/or **cocaine** users (last week use) recruited via community advertising and word of mouth (63% male, 46% Caucasian, 39% lifetime IDU, 28% current IDU [within prior 6 months])	Follow-up rate 75% at 24 months **HCV seroconversion**: NSD in rate of becoming HCV+ during the 24-month follow-up (5.0% vs 5.8%, p=0.80). NSD between ever injected drugs and never injected drugs participants. The annual HCV incident rate for injectors was 8.20 (95% CI 4.76-14.13) and for non-injectors was 0.74 (95% CI 0.19-2.98) per 100 person years. **Initiated IDU**: Of those reporting no lifetime IDU at baseline (n=168), fewer MI participants reported initiating IDU at 24 months (1.2 vs 11.9%, p=0.009) **Injection drug use frequency (days)**: NSD **Drug equipment sharing**: NSD	In Gilchrist 2017[14]

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Substance Abuse and Mental Health Services Administration. *Prevention and treatment of HIV among people living with substance use and/or mental disorders*. PEP20-06-03-001. Substance Abuse and Mental Health Services Administration (SAMHSA); 2020. Accessed July 13, 2022. https://store.samhsa.gov/sites/default/files/pep20-06-03-001.pdf

United Nations Office on Drugs and Crime, World Health Organization (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS). *HIV Prevention, Treatment, Care and Support for People Who Use Stimulant Drugs*. United Nations Office on Drugs and Crime; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf

Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.
Braunwarth W, Christ M, Dirks H, et al. *S3 Practice Guideline Methamphetamine-Related Disorders*. The Medical Center for Quality in Medicine (ÄZQ); 2016.
WHO. *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection*. World Health Organization; 2015. Accessed June 15, 2022. https://apps.who.int/iris/handle/10665/154590
Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):192. doi:10.15585/mmwr.rr7004a1

Non-Systematic Reviews

Source	Recommendation	Comments

Chan 2022[30]	Harm Reduction in Health Care Settings
	HARM REDUCTION FOR STIMULANT USE
	• Infection prevention for PWUD may include referral or integrating local syringe service program services into a clinical practice, counseling on safer injection practices (see Table 1), providing harm reduction, and offering PrEP
	• Know local and refer individuals to local resources such as Syringe services programs (SSPs), overdose prevention sites (OPS), and local harm reduction agencies.
	• For individuals who inject cocaine, the addition of an acidifier (eg, citric acid, vitamin C) is often required to dissolve the substance.[16] Over acidification of substance preparation has been hypothesized to play a role in venous sclerosis among PWID, causing scarring of small vessels, thereby driving individuals to switch to higher-risk injection site practices (eg, groin, neck vessels).[29] Patients should be counseled on using a minimal quantity of acidifier when dissolving substances and that ascorbic acid may be safer when compared with other acidifiers because of its safer pH.[29]
	Injection-Related Practices (p. 203)
	• **Peer educators**, defined as individuals with lived experience using substances, or who share other common characteristics/experiences with the person they are educating, may be another option if clinicians are not comfortable providing this counseling.
	• Clinicians can prescribe sterile syringes and needles for their patients to pharmacies
	• When sterile equipment is not available the CDC recommends disinfecting with bleach and the WHO "does not recommend that syringe disinfection with bleach be used as a primary HIV prevention strategy, unless syringe exchange programs are inaccessible, due to the lack of evidence of real-world effectiveness." (p. 204)
	• Do not lick needles before injecting
	Table 1. Summary of safer injection-related practices and supplies to discuss and personalize for people who inject drugs (p. 204)
	• Sterile equipment: Gold standard: use a new sterile needle and syringe every injection. If reusing equipment, clean with undiluted bleach as follows19:
	  ○ 1. Fill syringe with clean water, shake for 30 s, discard water from syringe
	  ○ 2. Fill syringe with bleach, shake for 30 s, discard bleach from syringe
	  ○ 3. Fill syringe with clean water, shake for 30 s, discard water from syringe	

	• Syringe size: U-100 insulin syringes (0.5 mL–1.0 mL) Tuberculin syringes
	• Needles: Smaller needle gauges (higher number gauge) are preferred because they create a smaller puncture wound and thus a lower infection risk
	  ○ Needle gauge for IV: 27G or 28G
	  ○ Needle gauge for IM: 21G or 23G (requires larger gauge needle)
	  ○ Needle length: 1/2 inch (12 mm) or 5/16 inch (8 mm)
	• Cookers and heat: Do not share cookers with others Heat a substance until bubbles form to decrease bacterial and fungal burden
	• Filters: Single-use filters to remove particulates Commercially produced "wheel" filters are preferred and can be purchased online without a prescription or found at local harm reduction agencies Single-use cotton balls when "wheel" filters unavailable
	• Dissolving substances: Use a sterile water supply If not available, use boiled water, bottled or tap water Use a minimal amount of acidifier to decrease risk of venous sclerosis Ascorbic acid (vitamin C) is the preferred acidifier over citric acid, fruit juices, and vinegar
	• Skin cleaning: Disinfect skin with alcohol, soap and water, or iodine before every injection
	• Fentanyl test strips: Test drugs before use (opioids and stimulants) Counsel patients on risk of false-negatives
	• Naloxone and setting: Carry naloxone and never use alone Leave naloxone in a visible location Leave door unlocked Use in location where one is comfortable and can take their time
	• Acidification: Ascorbic acid packets (vitamin C)	

	STI/HIV prevention programs for IDUs should emphasize **safer sex** as well as safer injection practices. injection drug use is independently associated with over twice the prevalence of STIs, and elevated risk is more likely attributed to higher rates of sex with infected partners rather than multiple partners or inconsistent condom use (Khan et al., 2013).	

Resources

Source	Resource	Comments
SAMHSA 2021 (existing guideline)	National Harm Reduction Coalition's Getting Off Right: A Safety Manual for Injection Drug Users (https://harmreduction.org/ issues/safer-drug-use/injection-safety-manual/)	Might be out of date
SAMHSA 2021 (existing guideline)	Boston Public Health Commission's Access Harm Reduction Overdose Prevention and Education Program Participant Guide (https://www. bphc.org/whatwedo/Recovery-Services/servicesfor-active-users/Documents/Client%20Manual%20 FINAL.pdf).	
SAMHSA 2020 (existing guideline)	Substance Abuse and Mental Health Services Administration. Prevention and treatment of HIV among people living with substance use and/or mental disorders. Publication No. PEP20-06-03-001.	
Grigg 2018 (existing guideline)	Safer Injecting This guide is aimed at people who inject drugs, to help reduce harm associated with injecting. www.drugs.ie/resourcesfiles/guides/ mqi_safer_injecting_guide.pdf	
	Skin cleaning protocol which emphasizes a two-step procedure, including an initial cleaning at the injection site with an alcohol pad using a back and forth method, followed by a second cleaning at the site using a circular motion." (Phillips 2013, p12)[3]	

	Public Health Department of Seattle & King County. (2002). All about abscesses. Public Health Department of Seattle & King County. https://kingcounty.gov/depts/health/communicable-diseases/hiv-std/patients/drug-use-harm-reduction.aspx	
	Harvey L, Boudreau J, Sliwinski SK, et al. Six Moments of Infection Prevention in Injection Drug Use: An Educational Toolkit for Clinicians. *Open Forum Infect Dis*. 2022;9(2):ofab631. https://doi.org/10.1093/ofid/ofab631	
	Needle cleaning protocol "three-sequence water and bleach rinse, following a revised version of a protocol endorsed by NIDA (Royer et al., 2004) and developed by Avants et al. (2004)" (Phillips 2013, p12)[3]	
	North American Syringe Exchange Network (NASEN) Directory locator map https://nasen.org/	Linked by CDC
	Look for something out of Rhode Island (Tracy Green)	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence for SE programs strong	Will vary based on some more nuanced injection practices (eg, crack cocaine)	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Negative bias or stigma associated with SE programs Excessive syringes in community, collect in abandoned houses Some community cost	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know

Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Clinical judgment (no evidence) ☐ Very low ☒ Low ☐ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
	Patients value outcomes, don't want to	☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*

		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	If the intervention being educated about is not available	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Harms associated with IDU are extremely high, other complications related to sharing needles/etc, risk of overdose higher
Benefits of safer injection practices also very high

When education is paired with other harm reduction practices, evidence is strong for a variety of outcomes. Education is an important component of change and relatively easy to implement; the importance of patient education is readily supported across a range of other medical conditions.

Subgroup Considerations

Patients with high readiness to change may have better outcomes.

Implementation Considerations

Safer injection practices:

- Using new, sterile syringes and injection equipment every time they inject
- Skin hygiene skills
- Rotating sites

Requires combining with other HR activities. Requires clinician knowledge and comfort with harm reduction principles

References

1. Substance Abuse and Mental Health Services Administration. *TIP 33: Treatment for Stimulant Use Disorders*. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004
2. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
3. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine Use, Methamphetamine Use Disorder, and Associated Overdose Deaths Among US Adults. *JAMA Psychiatry*. 2021;78(12):1329. doi:10.1001/jamapsychiatry.2021.2588
4. Imtiaz S, Strike C, Elton-Marshall T, Rehm J. Safer smoking kits for methamphetamine consumption. *Addiction*. 2020;115(6):1189-1190. doi:10.1111/add.14914
5. Khan MR, Berger A, Hemberg J, O'Neill A, Dyer TP, Smyrk K. Non-injection and injection drug use and STI/HIV risk in the United States: the degree to which sexual risk behaviors versus sex with an STI-infected partner account for infection transmission among drug users. *AIDS Behav*. 2013;17(3):1185-1194. doi:10.1007/s10461-012-0276-0
6. Copenhaver MM, Johnson BT, Lee IC, Harman JJ, Carey MP. Behavioral HIV risk reduction among people who inject drugs: Meta-analytic evidence of efficacy. *J Subst Abuse Treat*. 2006;31(2):163-171. doi:10.1016/j.jsat.2006.04.002
7. Johnson WD, Rivadeneira N, Adegbite AH, et al. Human Immunodeficiency Virus Prevention for People Who Use Drugs: Overview of Reviews and the ICOS of PICOS. *J Infect Dis*. 2020;222(Suppl 5):S278-S300. doi:10.1093/infdis/jiaa008
8. Puzhko S, Eisenberg MJ, Filion KB, et al. Effectiveness of Interventions for Prevention of Common Infections Among Opioid Users: A Systematic Review of Systematic Reviews. *Front Public Health*. 2022;10:749033. doi:10.3389/fpubh.2022.749033
9. Bahji A, Yanagawa B, Lamba W. Harm reduction for injection drug users with infective endocarditis: a systematic review. Can J Addict. (2020) 11:13–23. doi: 10.1097/CXA.0000000000000080
10. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *Int J Drug Policy*. 2014;25(1):34-52. doi:10.1016/j.drugpo.2013.07.001
11. Tilson H, Aramrattana A, Bozzette S, et al. *Preventing HIV Infection Among Injecting Drug Users in High-Risk Countries: An Assessment of the Evidence*. Institute of Medicine; 2007. doi:10.17226/11731
12. Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *J Infect Dis*. 2011;204(1):74-83. doi:10.1093/infdis/jir196
13. Gilchrist G, Swan D, Widyaratna K, et al. A systematic review and meta-analysis of psychosocial interventions to reduce drug and sexual blood borne virus risk behaviours among people who inject drugs. *AIDS Behav*. 2017;21(7):1791-1811. doi:10.1007/s10461-017-1755-0
14. Meader N, Li R, Jarlais DCD, Pilling S. Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users. *Cochrane Database Syst Rev*. 2010;(1). doi:10.1002/14651858.cd007192.pub2
15. Tran MTN, Luong QH, Le Minh G, Dunne MP, Baker P. Psychosocial Interventions for Amphetamine Type Stimulant Use Disorder: An Overview of Systematic Reviews. *Front Psychiatry*. 2021;12:512076. doi:10.3389/fpsyt.2021.512076
16. Rawson RA, Gonzales R, Pearce V, et al. Methamphetamine dependence and human immunodeficiency virus risk behavior. *J Subst Abuse Treat*. 2008;35(3):279-284. doi:10.1016/j.jsat.2007.11.003
17. Patnode CD, Perdue LA, Rushkin M, et al. Screening for Unhealthy Drug Use: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2020;323(22):2310. doi:10.1001/jama.2019.21381

18. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. *J Sex Res*. 2020;57(6):681-708. doi:10.1080/00224499.2020.1728514
19. Tran MTN, Luong QH, Le Minh G, Dunne MP, Baker P. Psychosocial Interventions for Amphetamine Type Stimulant Use Disorder: An Overview of Systematic Reviews. *Front Psychiatry*. 2021;12:512076. doi:10.3389/fpsyt.2021.512076
20. Smout M, Longo M, Harrison S, et al. The Psychostimulant Check-Up: A pilot study of a brief intervention to reduce illicit stimulant use. *Drug Alcohol Rev*. 2010;29(2):169-176. doi:10.1111/j.1465-3362.2009.00133.x
21. Stein MD, Herman DS, Anderson BJ. A Trial to Reduce Hepatitis C Seroincidence in Drug Users. *J Addict Dis*. 2009;28(4):389-398. doi:10.1080/10550880903183034
22. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 65. Prevention Injection Drug Use Kits

Recommendation: For patients who inject stimulants, clinicians should: provide or refer for safe injection supplies and harm reduction services.

Clinical Question Summary Table

Clinical Question	Are injection drug use kits effective for reducing harms related to injection drug use?
Population	Patients who inject stimulants
Intervention	Injection drug kits
Comparison	TAU (absence)
Main Outcomes	Harm reduction outcomes
Setting	Clinical settings
Background & Definitions	SSPs are associated with safer injection technique; fewer wounds; and reductions in HIV, HCV, other blood-borne infections, and complicated infections
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NSD**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
HIV infection transmission	N/A	Review of reviews: Palmateer 2022[1] (Supplementary)	**Evidence statement**: "The evidence is insufficient to either support or discount the effectiveness of sterile drug preparation equipment in the prevention of HIV." (p. 14) "On the basis of one weaker study, albeit with a positive result, we conclude that there is insufficient evidence" (p. 14) **Reviews/studies identified:** • No reviews identified • **1 study positive result** (serial cross-sectional): Fatseas 2012 (SCS, n=684 tx-seeking PWID OUD France, weaker) HIV prevalence decreased from 2 years before in the 4 years after sterile syringe kits made available (43.2% to 17.8%, p<0.0001)	SCS=serial cross-sectional
		Review of reviews:	**Evidence statement**: Insufficient evidence to either support or discount the effectiveness of provision of injection paraphernalia in reducing HIV transmission in PWID.	

		MacArthur 2014[2] (Supplementary)	**Reviews/studies identified:** • No reviews identified • No studies identified	
Hepatitis C infection transmission	N/A	Review of reviews: Palmateer 2022[1] (Supplementary)	**Evidence statement**: "The evidence is insufficient to either support or discount the effectiveness of sterile drug preparation equipment in the prevention of HCV." (p. 14) "On the basis of one weaker study with an equivocal result, we conclude that there is insufficient evidence" (p. 14) **Reviews/studies identified:** • No reviews identified • **1 study equivocal findings** (serial cross-sectional): Fatseas 2012 (SCS, n=684 tx-seeking PWID OUD France, weaker) NSD in HCV prevalence 2 years before and 4 years after sterile syringe kits made available (81.3% v 73.7%, p=0.1)	SCS=serial cross-sectional
		Review of reviews: MacArthur 2014[2] (Supplementary)	**Evidence statement**: Insufficient evidence to either support or discount the effectiveness of provision of injection paraphernalia in reducing HCV transmission in PWID. **Reviews/studies identified:** • 1 review: Gillies 2010: No evidence statement made • **1 study positive result** (1 cross-sectional): Morissette 2007 (CS)	CS=cross-sectional

Injection risk behaviors	N/A	Review of reviews: Palmateer 2022[1] (Supplementary)	**Evidence statement**: "Considering the evidence across the updated review and the 2011 RoR, the balance of the evidence is weighted heavily towards the positive studies, of which a good proportion have robust designs. Furthermore, the studies with equivocal findings are mostly of weaker designs. We conclude that there is sufficient evidence the effectiveness to support of sterile drug preparation equipment in the prevention of IRB." (p. 14) "On the basis of consistent evidence from a small number of robust studies or multiple weaker studies (in the absence of a review), we conclude that there is tentative evidence" (p. 14)
			Reviews/studies identified:
			• No reviews identified
			• 9 studies identified (n=6644, range 148-2037)
			  • **6 positive** (1 cohort, 1 cohort/cross-sectional, 2 cross-sectional, 2 serial cross-sectional): Patel 2018 (COH, robust design); Aspinall 2012 (CS, weaker design); Behrends 2017 (COH/CS, weaker design); Fatseas 2012 (SCS, weaker design); Kim 2015 (SCS, weaker design); Mehrabi 2020 (CS, weaker design)
			  • **1 mixed positive and equivocal results** (1 cross-sectional): Nazari 2016; Noroozi 2018; Rezaie 2017 [Note: counts as 1 study] (CS, weaker design) Equivocal for high vs low Ability to access NSPs; positive for high vs low use NSPs
			  • **2 equivocal** (2 cross-sectional): Naserirad 2020 (CS, weaker design); Welch-Lazoritz 2017 (CS, weaker design)
				COH=cohort CS=cross-sectional SCS=serial cross-sectional

		Review of reviews:	**Evidence statement**: Tentative evidence to support the effectiveness of drug preparation equipment provision in reducing IRB in people who inject drugs	

		MacArthur 2014[2] (Supplementary)	**Reviews/studies identified:**
			• 2 reviews identified:
			  ○ Gillies 2010: Evidence statement: **Tentative** evidence in support of the provision of sterile injecting paraphernalia
			  ○ Tilson 2007: No evidence statement made
			• 15 studies identified in reviews:
			  ○ **10 positive** (6 longitudinal cohort, 4 cross-sectional)
			  ○ **5 equivocal** (2 longitudinal cohort, 3 cross-sectional)	

[i:] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Core review: Identified in primary literature search

Supplementary reviews: Identified after primary literature search in a supplemental search. Source quality was not appraised for supplemental reviews

Individual Studies Findings

Study	Design	Intervention(s)	Participants	Outcomes	Comments
Morissett 2007[3] PMID 17689367	RCT Duration: Country: Setting:		N=275 IDUs		

Evidence-Based Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[4]	Harm Reduction in Health Care Settings HARM REDUCTION FOR STIMULANT USE Figure 2. Harm reduction kits for injection drug use can be distributed to patients and contain a variety of items for safer substance use. Items that can be included as part of this kit are listed. Depending on local use patterns, ascorbic acid packets may not be applicable. Adding wound care agents should also be considered, such as gauze, topical bacitracin, and BandAid. (p. 204) • 1.0 mL sterile syringes and needles (27 G-28G; length 12 mm or 8 mm length for IV use)	

	• Single use cooker • Sterile water and cotton balls (or wheel filters) • Tourniquet • Fentanyl test strips • Ascorbic acid packets • Alcohol prep pads • Wound care; Band-aid, bacitracin • Naloxone – IN or IM injector • Info on local harm reduction resources	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence very strong for needle exchange reducing HIV, Hep C, other blood-borne infections, safer injection technique, fewer wounds and complicated infections. One review of reviews found NSP's effect on HCV is tentative, HIV is sufficient, and IRB is sufficient. Provision of sterile preparation equipment on reducing HCV is insufficient, HIV is insufficient, IRB is sufficient	Coupling provision of providing safe injection supplies with other interventions such as providing linkage to treatment and medications for addition treatment (for co-occurring OUD) can increase the magnitude of desirable effects. Moderate to large for HIV Lower for HCV Large for IRB Probably moderate overall	☐ None ☐ Small ☒ Moderate ☐ Large ☒ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
No evidence of increased drug use, risky use, infection.	Concern with increasing IDU is not supported by the evidence. Bias and stigmatization of NSP clients.	☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison

		☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
	Depends on the specific outcome	☐ No evidence ☐ Very low ☐ Low ☒ Moderate ☐ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☒ Uncertain ☐ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Access to syringes is likely to have a larger impact on low health-service areas and populations.	☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
Uptake of using safe injection supplies by primarily cocaine injectors was low in one study.	Possibly a very high risk behavior population where the mere provision of safe supplies is less valued. Possible logistic issues. Patient and provider acceptability is likely high. Community buy in is a large barrier to implementing these programs.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies

***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	There are costs, but these are offset by reducing costly health problems.	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies

Conclusion

Justification

Harm reduction education related to injection drug use may include safer practices for preparing an injection, including using new supplies and clean surfaces, limiting overuse of acidifiers, and preventing injection site infections and vein damage

Subgroup Considerations

Access to syringes is likely to have a larger impact on low health-service areas and populations.

Implementation Considerations

Coupling provision of providing safe injection supplies with other interventions such as providing linkage to treatment and medications for addition treatment (for co-occurring OUD) can increase the magnitude of desirable effects.

References

1. Palmateer N, Hamill V, Bergenstrom A, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020). *Int J Drug Policy*. 2022;109:103872. doi:10.1016/j.drugpo.2022.103872
2. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *Int J Drug Policy*. 2014;25(1):34-52. doi:10.1016/j.drugpo.2013.07.001
3. Morissette C, Cox J, De P, et al. Minimal uptake of sterile drug preparation equipment in a predominantly cocaine injecting population: Implications for HIV and hepatitis C prevention. *Int J Drug Policy*. 2007;18(3):204-212. doi:10.1016/j.drugpo.2006.08.004
4. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 66. Prevention PrEP

Recommendation: Clinicians should offer HIV PrEP to patients who use stimulants and are at increased risk for HIV, including those who:

1. engage in risky sexual behavior,
2. access postexposure prophylaxis (PEP) regularly, and/or
3. inject drugs.

Clinical Question Summary

Clinical Question	What factors should be considered when determining the appropriateness of HIV PrEP for patients with StUD?
Population	HIV-uninfected individuals who misuse stimulants
Intervention	Antiretroviral pre-exposure prophylaxis (PrEP) for HIV: daily or intermittent oral tenofovir disoproxil fumarate (TDF) alone or plus emtricitabine (FTC)
Comparison	TAU
Main Outcomes	Human Immunodeficiency Virus (HIV) infection
Setting	Clinical settings
Background & Definitions	Notes: • "The addition of stimulant use as a criterion guiding PrEP prescription or implementing substance use campaigns might be warranted in MSM and trans women, as has occurred in some settings in Australia and the USA.134" (Farrell 2019, p10)[1] • While mixed (Goodman-Meza 2019), there is some evidence that MSM/TW who use stimulants have lower PrEP adherence compared to MSM/TW who do not (Hojilla 2018; 2019). However, modeling indicates that while lower adherence might decrease the relative effectiveness of a program prioritizing MSM/TW who use stimulants, the strategy would still likely prevent a higher number of new infections (Farrell 2019)[1]. • Among sexual minority men "There were 18 studies that examined associations of stimulants, chemsex drug use, or club drug use with PrEP adherence. More than two-thirds of these studies (n = 13) found that stimulants, chemsex drugs, or club drug use were associated with lower PrEP adherence. In contrast, three studies documented associations of stimulant use or chemsex drug use with better PrEP adherence, particularly in the context of recent CAS." (Viamonte et al., 2022, p. 238)[2]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **MSM**: Men who have sex with men, **N**: Number, **PrEP**: pre-exposure prophylaxis for HIV, **PWID**: People who inject drugs, **RCT**: Randomized Control Trial, **SMM**: Sexual minority men, **StUD**: Stimulant use disorder, **TDF-FTC:** tenofovir disoproxil fumarate-emtricitabine
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Summary of Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
HIV infection transmission	N/A	Meta-analysis: Murchu 2022[3] (Not assessed)	Overall sample • PrEP is effective in preventing HIV acquisition in 13 RCTs (k=26759, 1.6% vs 2.5%, RR=0.41 [0.26, 0.67], p<0.001) with significant heterogeneity (I^2=79%, p<0.001). MSM • High quality evidence that PrEP is effective in preventing HIV acquisition in MSM with a rate reduction of 75% based on 6 RCTs (k=5103, RR=0.25 [95% CI 0.1, 0.61]). PrEP users had a 3% lower rate of HIV acquisition per person-year of follow-up (absolute rate difference RD= −0.03 [−0.01, −0.05]). Serodiscordant couples • High quality evidence that PrEP (daily oral) is effective in preventing HIV acquisition in serodiscordant couples with a rate reduction of 75% based on 2 RCTs (n couples=4819, k=5237, RR=0.25 [0.14, 0.46]; RD= −0.01 [−0.01, −0.02] Heterosexuals • Low quality evidence that PrEP is not effective in preventing heterosexual HIV transmission based on 4 RCTs (k=6821, p-0.32) with significant heterogeneity (I^2=66%, p=0.03). 3 trials had low (<80%) adherence. People who inject drugs (PWID) • Moderate quality evidence that PrEP is effective in preventing HIV transmission in PWID with a rate reduction of 49% based on 1 RCT (k=9666, RR=0.51 [0.29, 0.92]; RD= −0.00 [−0.00, −0.01]. Study had low (<80%) adherence. • Choopanya 2013 (n=2413, daily oral tenofovir)	Oral PrEP to prevent HIV in all populations Substance use was not an inclusion criterion. k=person-years of follow-up RR= rate ratio RD=absolute rate difference
		Review of reviews: Farrell 2019[1] (Not assessed)	Among people who inject drugs (PWID): **PrEP for HIV** decreased HIV incidence in one review (48.9% [9.6, 72.2]). Grade B† evidence: evidence from one or two randomized controlled trials only. †Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically.	Review focused on **stimulant related** harms

			• Martin M, Vanichseni S, Suntharasamai P, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. *AIDS*. 2015;29:81924. [PubMed: 25985403]	
		Meta-analysis: Okwundu 2012[4] (Not assessed)	**TDF+ FTC > Placebo:** TDF+ FTC showed a reduction in the risk of acquiring HIV infection in 4 RCTs (8813 participants, RR=0.49 [0.28, 0.85], p=0.01). Substantial heterogeneity (I^2 =77%, p=0.005) Moderate quality evidence • Baeten 2012, Grant 2010, Thigpen 2012, Van Damme 2012. Among high-risk heterosexuals (serodiscordant couples and sexually active young people in a high-risk region): • TDF+ FTC > Placebo: **Trend** for TDF+ FTC to have a greater reduction in the risk of acquiring HIV infection in 3 RCTs (n= 6419, RR= 0.46 [0.19, 1.10], p=0.08). Substantial heterogeneity (I^2 =84%, p<0.001) o Baeten 2012, Thigpen 2012, Van Damme 2012) Among MSM: • **TDF+ FTC > Placebo:** TDF+ FTC showed a reduction in the risk of acquiring HIV infection in 1 RCT (n=2499, RR= 0.56 [0.38, 0.84], p<0.001) o Grant 2010 **TDF > Placebo:** TDF+ FTC showed a significant reduction in the risk of acquiring HIV infection in 2 RCTs (4027 participants, RR= 0.33 [0.20, 0.55], p<0.001). Moderate quality evidence • Baeten 2012, Peterson 2007 **TDF+FTC vs TDF alone** did not differ in HIV acquisition in 1 RCT (n= 3163, p=0.372) • Baeten 2012	Cochrane review of PrEP for preventing HIV in high-risk individuals Substance use was not an inclusion criterion. "further studies are need to evaluate the method of administration (daily versus intermittent dosing), long-term safety and cost effectiveness of PrEP in different risk groups and settings." (p. 2)
Sexually transmitted infection transmission	N/A	Meta-analysis: Traeger 2018[5] (Not assessed)	Among MSM and transgender women: • **Trend** towards PrEP use to be associated with an increased incidence for any STI diagnosis (8 studies, 4388 participants, OR=1.24 [95% CI 0.99–1.54], p=0.052), with moderate heterogeneity (I^2=50%, p=0.052). • PrEP was associated with **increased incidence** of any rectal STI diagnosis (4 studies, OR=1.39 [1.03, 1.87, p=0.03), particularly rectal chlamydia (4 studies, OR=1.59 (1.19–2.13), p=0.002). • Condom use rates remain stable (see below), suggesting any risk compensation behavior is happening among MSM engaged in unprotected sex prior to PrEP use.	Effects of PrEP for the Prevention of HIV Infection on Sexual Risk Behavior in MSM Substance use was not an inclusion criterion.

		Review of reviews: Farrell 2019[1] (Not assessed)	Among people who inject drugs (PWID): **PrEP for HIV** had **no effect** on STI incidence in 2 reviews (no pooled estimate reported). Grade B† evidence: evidence from one or two randomized controlled trials only. †Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically. • Escudero DJ, Lurie MN, Kerr T, Howe CJ, Marshall BD. HIV pre-exposure prophylaxis for people who inject drugs: a review of current results and an agenda for future research. *J Int AIDS Soc.* 2014;17:18899. [PubMed: 24679634] • Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381:2083-2090. [PubMed: 23769234] **PrEP for STIs decreased incidence** of STIs (OR 0.27 [0.09, 0.83]). Grade B† evidence: evidence from one or two randomized controlled trials only. †Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically. • Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIVinfected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis.* 2015;42: 98-103. [PubMed: 25585069]	Review focused on **stimulant related** harms
Injection risk behaviors	N/A	Review of reviews: Farrell 2019[1] (Not assessed)	Among people who inject drugs (PWID): PrEP for HIV had **no effect** on injection risk behaviors in 2 reviews (no pooled estimate reported). Grade B† evidence: evidence from one or two randomized controlled trials only. †Evidence drawn from people who inject drugs and not specifically those who use stimulants; however, we have no reason to believe this intervention would operate differently in people who use stimulants specifically. • Escudero DJ, Lurie MN, Kerr T, Howe CJ, Marshall BD. HIV pre-exposure prophylaxis for people who inject drugs: a review of current results and an agenda for future research. *J Int AIDS Soc*. 2014;17:18899. [PubMed: 24679634] • Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised,	Review focused on **stimulant related** harms

			doubleblind, placebo-controlled phase 3 trial. *Lancet.* 2013; 381: 2083-2090. [PubMed: 23769234]	
Condom use	N/A	Meta-analysis: Traeger 2018[5] (Not assessed)	Among MSM and transgender women: PrEP use was **not associated** with decreased condom use rates in any of the 13 studies found (5008 participants). No meta-analysis conducted.	Effects of PrEP for the Prevention of HIV Infection on Sexual Risk Behavior in MSM Substance use was not an inclusion criterion.
Willingness to use PrEP	N/A	Meta-analysis: Sun 2022[6] (Critically low)	Among MSM and transgender women: • Pooled proportion of MSM willing to use PrEP was moderate (165 data points, 266,135 participants, 58.6% [54.8, 62.4], p<0.001). • Willingness in high income countries (100 data points, 55.1% [50.5, 59.7%]) lower than in middle- and low-income countries (p=0.03). • MSM in high incidence groups (128 data points, 61.2% [57.7, 64.6] were more willing to use PrEP (p = 0.003). • No significant difference in willingness to use PrEP between MSM and transgender populations (10 TG datapoints, p=0.13). • The main facilitators of willingness to use PrEP were PrEP awareness, condomless sexual behaviors, high perceived risk of HIV infection and influence of social network. The main barriers were doubts about the efficacy and side effects of PrEP.	Awareness of and willingness to use HIV PrEP among MSM. Substance use was not an inclusion criterion.
Awareness of PrEP	N/A	Meta-analysis: Sun 2022[6] (Critically low)	Among MSM and transgender women: • Pooled proportion of MSM aware of PrEP was low (145 data points, 261,041 participants, 50% [44.8, 55.2], p<0.001) with high heterogeneity (I^2=99.9%, p<0.001). • Awareness in high income countries (93 data points, 57.2% [50.6, 63.8]) lower than in middle- and low-income countries (p<0.001).	Awareness of and willingness to use HIV PrEP among MSM. Substance use not an inclusion criterion.
Serious adverse events	N/A	Meta-analysis: Murchu 2022[3] (Not assessed)	High quality evidence from 12 RCTs that serious adverse events do not occur more commonly in patients taking PrEP compared with placebo (k=17778, p-0.39). Serious adverse events occurred in 7% of patients in trials but most were not study-drug related. No deaths were related to PrEP.	Oral PrEP to prevent HIV in all populations. Substance use was not an inclusion criterion. k=person-years of follow-up
		Meta-analysis: Okwundu 2012[4] (Not assessed)	There were no significant differences in the risk of adverse events across all the studies that reported on adverse events. **TDF+ FTC vs Placebo:** Moderate quality evidence based on 3 RCTs of 6862 participants (Baeten 2012, Grant 2010, Thigpen 2012) **TDF vs Placebo:** Moderate quality evidence based on 1 RCT of 3168 participants (Baeten 2012) **TDF+ FTC vs TDF alone**: 1 RCT with 3163 participants (Baeten 2012)	Cochrane review of PrEP for preventing HIV in high-risk individuals Substance use was not an inclusion criterion.

Adverse events	N/A	Meta-analysis: Murchu 2022[3] (Not assessed)	High quality evidence from 10 RCTs that adverse events do not occur more commonly in patients taking PrEP compared with placebo (k=17358, p=0.37. Adverse events were common in trials (78% of patients reporting 'any' event).	Oral PrEP to prevent HIV in all populations. Substance use was not an inclusion criterion. k=person-years of follow-up

[i] The strength of evidence (SOE) is classified as follows: High = further research is very unlikely to change our confidence on the estimate of effect. Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ii: Quality of meta-analyses and systematic reviews evaluated using AMSTAR-2 instrument: Shea et al (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ, 358,* j4008.

Characteristics of Individual Studies Table

Source	Design	Intervention/ Comparator(s)	Participants	Outcomes	Comments
Gilkey 2019[7]	Qualitative interview 2013-2014 USA	Using HIV risk screening tools to identify candidates for PrEP	n=23 adult MSM reporting HIV risk behaviors in previous 3 months, n=12 PCPs specializing in care of MSM, n=19 PCPs in general practice. All recruited from academic medical center or LGBTQ community health center.	**Anticipated impact of receiving a high HIV risk score**: Most MSM reported they would seek to reduce their risk by: considering PrEP, changing their sexual behavior to use condoms more frequently or have fewer partners. A small proportion of MSM reported they would not change their behavior. A few reported they would feel anxiety and fear.	
Goodman-Meza 2019[8]	Longitudinal USA	PrEP	MSM stimulant users with multiple condomless sex partners	**PrEP adherence:** Good adherence to PrEP	
Hojilla 2019[9]	open label		MSM/TW	**PrEP adherence** (plasma tenofovir concentrations): Lower adherence who use stimulants compared to those who do not **Cocaine use** (hair testing)	Hojilla JC, Satre DD, Glidden DV, et al. Brief Report: Cocaine Use and Pre-exposure Prophylaxis: Adherence, Care Engagement, and Kidney Function. J Acquir Immune Defic Syndr 2019; 81(1): 78-82.

Hojilla 2018[10]				**PrEP adherence:** Lower adherence to PrEP among MSM/TW who use stimulants compared to those who do not	Hojilla JC, Vlahov D, Glidden DV, et al. Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis. J Int AIDS Soc 2018; 21(3): e25103.
Towe 2021[11]	Cross-sectional survey Country: USA Setting: Community		N=352 HIV negative individuals recruited from the community who reported stimulant use in the past month, primarily cocaine	• Over half the sample (60%) met criteria for PrEP candidacy • Only 14% of the sample had ever heard of PrEP • Willingness to take PrEP (1-10 point scale), Mean (sd) = 7.78 (3.22) • Half (56%) selected the highest possible rating	sample included very few MSM

Existing Guidelines

Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

Centers for Disease Control and Prevention. *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2021 Update: A Clinical Practice Guideline*. Centers for Disease Control and Prevention (CDC); 2021:108.

United Nations Office on Drugs and Crime, World Health Organization (WHO), and Joint United Nations Programme on HIV/AIDS (UNAIDS). *HIV prevention, treatment, care and support for people who use stimulant drugs*; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf

World Health Organization. *Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach*. No. 1035. World Health Organization (WHO); 2021. Accessed June 15, 2022. https://apps.who.int/iris/handle/10665/351172

US Preventive Services Task Force, Owens, DK, Davidson KW, Krist AH, et al. Preexposure Prophylaxis for the Prevention of HIV Infection: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2019;*321*(22):2203. https://doi.org/10.1001/jama.2019.6390

Non-Systematic Reviews

Source	Recommendation	Comments
Chan 2022[12]	**Harm Reduction in Health Care Settings** HUMAN IMMUNODEFICIENCY VIRUS PREVENTION: PREEXPOSURE PROPHYLAXIS	

	• The CDC recommends offering PrEP to individuals with injection behaviors that places them at an increased risk of acquiring HIV, which includes any sharing of injection or drug preparation equipment in the past 6 months, or risk of sexual acquisition.33 Clinicians should offer PrEP to qualifying PWID. (p. 206) Table 2. The basics of prescribing preexposure prophylaxis for patients (p. 207) adapted from Preventing new HIV infections j| Guidelines and recommendations | HIV/AIDS |CDC. 2020. Available at: https://www.cdc.gov/hiv/guidelines/preventing.html. Accessed December 26, 2020. Prescribing PrEP (Once-Daily TDF-FTC 300–200 mg) • Indications: •People who inject drugs •MSM •HIV-positive partner •Inconsistent condom use •Recent sexually transmitted infection •Commercial sex work • Contraindications Acute or chronic HIV infection Creatinine clearance <60 mL/min • Counsel on side effects Short term: nausea Long term: potential renal dysfunction, potential bone demineralization • Baseline laboratory test results •HIV antigen/antibody test; if symptoms of acute HIV infection test for HIV RNA •Creatinine •Hepatitis B surface antibody and antigen •Hepatitis C antibody •Syphilis, gonorrhea, chlamydia (3-site testing at the urethral, rectal, and pharyngeal sites for MSM) •Urinalysis for glucose and protein •Urine pregnancy test • Vaccines: Hepatitis B if not immune • Follow-up visits: Every 3 mo • Follow-up laboratory test results: •HIV antigen/antibody test; every 3 mo; if symptoms of acute HIV infection test for HIV RNA •Creatinine clearance at 3 mo and every 6 mo thereafter •Sexually transmitted infection screening every 3–6 mo •Urine pregnancy test every 3 mo	

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Substantial high quality evidence that PrEP prevents HIV overall and consistently across sub-groups.	While not tested in a stimulant using population, substantial benefits are still expected in this group. Also, there is high levels of stimulant use in some of the sub-groups examined (eg, MSM).	☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know

Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
PrEP does not seem to decrease condom use or increase injection risk behavior. Rate of serious adverse effects are low, and reversed after discontinuation (see Summary Table). Side effects are primarily gastrointestinal, nausea, headaches. Generally mild.		☐ None ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
	While there are some undesirable side-effects, preventing HIV is a critically important outcome.	☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No evidence ☐ Very low ☐ Low ☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☒ Probably no ☐ No ☐ Varies
***Equity**: What would be the impact on health inequities?		

Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☒ Probably reduced ☐ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

Strong evidence exists that PrEP is effective at preventing HIV overall, as well as consistently across subgroups with the highest risk for HIV

Subgroup Considerations

None noted

Implementation Considerations

Side effects are primarily gastrointestinal, nausea, headaches, and are generally mild.

References

1. Farrell M, Martin NK, Stockings E, et al. Responding to global stimulant use: challenges and opportunities. *Lancet*. 2019;394(10209):1652-1667. doi:10.1016/S0140-6736(19)32230-5
2. Viamonte M, Ghanooni D, Reynolds JM, Grov C, Carrico AW. Running with Scissors: a Systematic Review of Substance Use and the Pre-exposure Prophylaxis Care Continuum Among Sexual Minority Men. *Curr HIV/AIDS Rep*. 2022;19(4):235-250. doi:10.1007/s11904-022-00608-y
3. Murchu E, Marshall L, Teljeur C, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. *BMJ Open*. 2022;12(5):e048478. doi:10.1136/bmjopen-2020-048478
4. Okwundu CI, Uthman OA, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. Cochrane HIV/AIDS Group, ed. *Cochrane Database Syst Rev*. Published online July 11, 2012. doi:10.1002/14651858.CD007189.pub3
5. Traeger MW, Schroeder SE, Wright EJ, et al. Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2018;67(5):676-686. doi:10.1093/cid/ciy182
6. Sun Z, Gu Q, Dai Y, et al. Increasing awareness of HIV pre-exposure prophylaxis (PrEP) and willingness to use HIV PrEP among men who have sex with men: a systematic review and meta-analysis of global data. *J Int AIDS Soc*. 2022;25(3). doi:10.1002/jia2.25883
7. Gilkey MB, Marcus JL, Garrell JM, Powell VE, Maloney KM, Krakower DS. Using HIV Risk Prediction Tools to Identify Candidates for Pre-Exposure Prophylaxis: Perspectives from Patients and Primary Care Providers. *AIDS Patient Care STDs*. 2019;33(8):372-378. doi:10.1089/apc.2019.0056
8. Goodman-Meza D, Beymer MR, Kofron RM, et al. Effective use of pre-exposure prophylaxis (PrEP) Among stimulant users with multiple condomless sex partners: a longitudinal study of men who have sex with men in Los Angeles. *AIDS Care*. 2019;31(10):1228-1233. doi:10.1080/09540121.2019.1595523
9. Hojilla JC, Satre DD, Glidden DV, et al. Brief Report: Cocaine Use and Pre-exposure Prophylaxis: Adherence, Care Engagement, and Kidney Function. *J Acquir Immune Defic Syndr.* 2019; 81(1): 78-82. https://doi.org/10.1097/QAI.0000000000001972
10. Hojilla JC, Vlahov D, Glidden DV, et al. Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis. *J Int AIDS Soc.* 2018;21(3):e25103. https://doi.org/10.1002/jia2.25103
11. Towe SL, Sullivan CA, McKellar MS, Meade CS. Examining the Potential of Pre-exposure Prophylaxis (PrEP) for HIV Prevention in a Community Sample of Persons Who Use Stimulants Living in the Southern United States. *AIDS Behav*. 2021;25(5):1480-1489. doi:10.1007/s10461-020-02987-y
12. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

Table 67. Prevention Oral Health

Recommendation: People who use stimulants are at high risk of dental complications, such as poor dentition, dental carries, abscesses, as well as subsequent malnutrition. Clinicians should:

1. encourage patients who use stimulants to maintain good oral hygiene and receive regular dental care, and
2. offer referrals to a dental care provider if needed.

Clinical Question Summary

Clinical Question	What interventions are effective for preventing oral health-related harms in patients with StUD?
Population	People who use stimulants
Intervention	Encourage oral hygiene and refer to dental care
Comparison	TAU (absence)
Main Outcomes	Improved oral health outcomes
Setting	Clinical settings
Background & Definitions	Notes: • MA-dependent adults (N = 301) interviewed and examined 3 years after treatment. Among the most frequently reported lifetime conditions were severe dental problems (33%, N = 99). intravenous MA use was significantly associated with missing teeth (odds ratio = 2.4; 95% confidence interval, 1.2-4.7) (Mooney 2009)[1] • (Marques 2015)[2] • "ATS use has been associated with dental decay and dental diseases, although it is unclear how much of this is a direct result of (meth)amphetamine use or related to poor diet and personal oral and dental hygiene (Grund et al. 2010)." (Rigoni 2018 p19)[3] • Type of drug used was related with odds of periodontal disease and decayed, missing, and filled teeth (DMFT) (Yazdanian 2020)[4] • Systematic review of guidelines (Osborne 2022)[5] • Crack-cocaine use was associated with poor oral health (4 studies) compared to the general population in meta-analysis (Butler 2017)[6]
Abbreviations	**ATS:** Amphetamine-type stimulant, **ATStUD**: Amphetamine-type stimulant use disorder, **CoUD**: Cocaine use disorder, **MA:** Methamphetamine, **MaUD**: Methamphetamine use disorder, **N**: Number, **NDS**: No significant difference, **RCT**: Randomized Control Trial, **StUD**: Stimulant use disorder
Conflict of Interest	COIs of all Clinical Guideline Committee (CGC) members were assessed and managed by ASAM's QIC following an established procedure in accordance with ASAM's COI policy.

Evidence Profile

Systematic Review and Meta-Analysis Findings

Outcome	Strength of Evidence[i]	Source (Quality[ii])	Effect/Impact	Comments
Critical/Important Outcomes				
Gingivitis	N/A	Meta-analysis: Werner 2016[7] (Not assessed)	9 RCTs of psychological and/or behavioral interventions vs traditional oral health education/information in were found. **No significant differences** in gingivitis presence (Löe and Silness 1963 gingival index) as mean proportion of measured tooth surfaces (p=0.26) with significant heterogeneity (I^2=92%, p<0.001). • Jönsson 2006 (n=35 Sweden, client self-care commitment model [CSCCM] vs TAU) • Jönsson 2009 (n=113 Sweden, individually tailored oral health educational program [ITOHEP] vs TAU vs ITOHP+TAU)	adults or adolescents (age ≥13) with poor oral health (defined as dental caries, periodontal disease, and/or peri-implantitis)
Bleeding on probing	N/A	Meta-analysis: Werner 2016[7] (Not assessed)	**No significant differences** in bleeding on probing as mean proportion (%) of measured tooth surfaces. plaque presence (p=0.67) with significant heterogeneity (I^2=81%, p=0.001). • Brand 2013 (n=56 US, brief motivational interviewing [BMI] vs TAU) • Jönsson 2006 (n=35 Sweden, client self-care commitment model [CSCCM] vs TAU) • Jönsson 2010 (n=113 Sweden, individually tailored oral health educational program [ITOHEP] vs TAU vs ITOHP+TAU) • Stenman 2012 (n=44 Sweden, motivational interviewing [MI] vs TAU)	
Plaque	N/A	Meta-analysis: Werner 2016[7] (Not assessed)	**No significant differences** in plaque presence as mean proportion (%) of measured tooth surfaces (p=0.18) with significant heterogeneity (I^2=81%, p=0.006). • Godard 2011 (n=51 France, motivational interviewing [MI] vs TAU) • Kakudate 2009 (n=38 Japan, Farquhar's 6-step method vs TAU) • Stenman 2012 (n=44 Sweden, motivational interviewing [MI] vs TAU) **Intervention** led to lower plaque presence (Silness and Löe 1964 plaque index) as mean proportion of measured tooth surfaces compared to TAU in 3 RCTs (MD= -0.24 [-0.41, -0.06], p=0.008) with significant heterogeneity (I^2=89%, p<0.001). • Jönsson 2006 (n=35 Sweden, client self-care commitment model [CSCCM] vs TAU) • Jönsson 2009 (n=113 Sweden, individually tailored oral health educational program [ITOHEP] vs TAU vs ITOHP+TAU) • Pilloppot 2005 (n=33, behavioral/motivational education vs TAU) 4 RCTs were not included in meta-analysis due to measure heterogeneity.	

			• 2 RCTs found intervention led to improvements in plaque presence compared to TAU: o Little 1997 (n=107 US, freedom from plaque [FFP] vs TAU) o Jönsson 2010 (n=113 Sweden, individually tailored oral health educational program [ITOHEP] vs TAU vs ITOHP+TAU) • 2 RCTs found no significant differences: o Brand 2013 (n=56 US, brief motivational interviewing [BMI] vs TAU) o Tedesco 1992 (n=167 US, social cognitive intervention [SCI] vs TAU vs SCI+TAU	
Oral health behaviors	N/A	Meta-analysis: Werner 2016[7] (Not assessed)	No meta-analysis for this outcome due to measure heterogeneity. **Intervention** led to improvements in self-reported oral health behaviors measured as interdental cleaning and toothbrushing compared to TAU in 3 RCTs. • Jönsson 2006 (n=35 Sweden, client self-care commitment model [CSCCM] vs TAU) • Jönsson 2009 (n=113 Sweden, individually tailored oral health educational program [ITOHEP] vs TAU vs ITOHP+TAU) • Kakudate 2009 (n=38 Japan, Farquhar's 6-step method vs TAU)	

Individual Studies Findings

Study	Design	Intervention/ Comparator(s)	Participants	Outcomes	Comments
Cury 2018[8]	Cross-sectional		Men	Association between oral mucosal lesions and crack and powder cocaine addiction	
Hegazi 2021[9]	Cross-sectional	Calibrated dentists assessed periodontal disease, untreated caries, and missing teeth	N=8762 Participants of the National Health and Nutrition Examination Survey aged 30-64 who completed a periodontal examination and self-reported lifetime and/or recent MA use.	MA users had a higher prevalence of dental caries and periodontal disease compared to those that had never used MA. Taking MA orally and/or through injection was associated with higher odds of severe periodontitis than orally only (AOR: 3.72; CI: 1.79 – 7.75).	
Rommel 2016[10]	Case-control Germany		N=200; 100 MA users + 100 matched-pair controls. MA users were recruited at one of two specialist clinics for addiction medicine during dental health clinics. Age and gender matched	MA users had a higher prevalence of dental caries, gingivitis, and periodontal disease compared to a age and gender-matched controls who have never used MA. MA	"we recommend a specific prevention and therapeutic concept including educational campaigns for MA users and specialized dental care for CM patients." (p. 469)

			pairs were randomly selected from hospitalized patients at a University Hospital and from patients of two ambulatory dental surgeries.	users also had significantly poorer oral hygiene and plaque.	
Shetty 2016[11]				Propensity score analysis demonstrates increased dental disease among MA users	
Smit & Naidoo 2015[12]	Cross-sectional South Africa		N=308 self-reported MA users presenting at 22 specialized substance addiction treatment canters	MA users brushed their teeth significantly less often ($p < 0.001$; $\chi2 = 23.84$; OR = 3.25). There is a significant positive relationship between duration of drug use and mean number of decayed teeth ($p = 0.007$; $\chi2 = 12.07$).	"When methamphetamine abuse is detected, the dentist can play a key role in early management of drug addiction by referring the patient to specialised substance addiction treatment centres. In addition, by restoring the dental appearance, users may regain their self-esteem and improve their oral health quality of life." (p. 531)

Spolsky 2018[13]	Cross-sectional		N=546 adult MA users recruited via community outreach and snowball sampling in Los Angeles, CA. Sample also had high incidence of current smoking (68.9%)	- Prevalence of periodontitis
				  - Mild: 6 (1.7) %(sd)
				  - Moderate: 54.8 (2.1) %(sd)
				  - Severe: 22.9 (1.8) %(sd)
				MA use contributes to increased risk of disease, but other (behavioral) factors such as smoking contribute to risk of severe disease.	

Existing Guidelines

- Grigg J, Manning V, Arunogiri S, et al. *Methamphetamine Treatment Guidelines: Practice Guidelines for Health Professionals*. 2nd ed. Turning Point; 2018.
- Braunwarth W, Christ M, Dirks H, et al. S3 Practice Guideline Methamphetamine-Related Disorders. The Medical Center for Quality in Medicine (ÄZQ); 2016. www.crystal-meth.aezq.de
- Substance Abuse and Mental Health Services Administration. *Treatment Improvement Protocols (TIP) 33: Treatment for Stimulant Use Disorders*. PEP21-02-01004. Substance Abuse and Mental Health Services Administration (SAMHSA); 2021. Accessed July 13, 2022. https://store.samhsa.gov/product/treatment-for-stimulant-use-disorders/PEP21-02-01-004

- United Nations Office on Drugs and Crime, World Health Organization (WHO), and Joint United Nations Programme on HIV/AIDS (UNAIDS). HIV prevention, treatment, care and support for people who use stimulant drugs; 2019. Accessed August 1, 2021. https://www.unodc.org/documents/hiv-aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf

Evidence to Decision (EtD) Table

Desirable Effects: How substantial are the desirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
Pharmacological mechanism for dental caries and problems in PWU stimulant, also lifestyle, diet, SES		☐ None ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know
Undesirable Effects: How substantial are the undesirable anticipated effects of the intervention?		
Evidence Summary	*Additional Considerations*	*Judgment*
	None	☒ None ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know
Balance of Effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☒ Substantially favors intervention ☐ Somewhat favors intervention ☐ Favors neither ☐ Somewhat favors comparison ☐ Substantially favors comparison ☐ Varies ☐ Don't know
Certainty/Quality of Evidence: What is the overall certainty of the evidence of effects? Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)		
Evidence Summary	*Additional Considerations*	*Judgment*
Evidence is indirect, based on extrapolation	Clinical judgment supports	☐ No evidence ☐ Very low ☐ Low

		☐ Moderate ☒ High
***Values and preferences:** Is there important uncertainty about how much people value the main outcomes? Confidence in values and preferences and their variability.		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Yes ☐ Possibly yes ☐ Uncertain ☐ Probably no ☒ No ☐ Varies
***Equity**: What would be the impact on health inequities?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies
***Acceptability**: Is the option acceptable to key stakeholders?		
Evidence Summary	*Additional Considerations*	*Judgment*
		☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies
***Feasibility:** Is the option feasible for patients, caregivers, and providers to implement?		
Evidence Summary	*Additional Considerations*	*Judgment*
	Making referrals is challenging, particularly if medicare/medicaid/self-pay Straightforward to encourage good oral care etc., follow through on referrals more challenging	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Conclusion

Justification

People who use stimulants are well known to be at high risk of dental complications—such as poor dentition, dental caries, and abscesses—and poor oral health is associated with subsequent malnutrition

Subgroup Considerations

None noted

Implementation Considerations

Many insurance plans do not adequately cover dental care, and clinicians need to be aware of local resources to make referrals

References

1. Mooney LJ, Glasner-Edwards S, Marinelli-Casey P, et al. Health conditions in methamphetamine-dependent adults 3 years after treatment. *J Addict Med*. 2009;3(3):155-163. doi:10.1097/ADM.0b013e3181a17c79
2. Marques TCN, Sarracini KLM, Cortellazzi KL, et al. The impact of oral health conditions, socioeconomic status and use of specific substances on quality of life of addicted persons. *BMC Oral Health*. 2015;15(1):38. doi:10/gb5kds
3. Rigoni R, Breeksema J, Woods S. *Speed Limits: Harm Reduction for People Who Use Stimulants*.; 2018.
4. Yazdanian M, Armoon B, Noroozi A, et al. Dental caries and periodontal disease among people who use drugs: a systematic review and meta-analysis. *BMC Oral Health*. 2020;20(1):44. doi:10/gn764d
5. Osborne B, Larance B, Ivers R, Deane FP, Robinson LD, Kelly PJ. Systematic review of guidelines for managing physical health during treatment for substance use disorders: Implications for the alcohol and other drug workforce. *Drug Alcohol Rev*. 2022;41(6):1367-1390. doi:10.1111/dar.13504
6. Butler AJ, Rehm J, Fischer B. Health outcomes associated with crack-cocaine use: Systematic review and meta-analyses. *Drug Alcohol Depend*. 2017;180:401-416. doi:10.1016/j.drugalcdep.2017.08.036
7. Werner H, Hakeberg M, Dahlström L, et al. Psychological Interventions for Poor Oral Health: A Systematic Review. *J Dent Res*. 2016;95(5):506-514. doi:10.1177/0022034516628506
8. Cury PR, Araujo NS, das Graças Alonso Oliveira M, dos Santos JN. Association between oral mucosal lesions and crack and cocaine addiction in men: a cross-sectional study. *Environ Sci Pollut Res*. 2018;25(20):19801-19807. doi:10.1007/s11356-018-2120-1
9. Hegazi F, Alhazmi H, Abdullah A, et al. Prevalence of oral conditions among methamphetamine users: NHANES 2009–2014. *J Public Health Dent*. 2021;81(1):21-28. doi:10.1111/jphd.12389
10. Rommel N, Rohleder NH, Wagenpfeil S, et al. The impact of the new scene drug “crystal meth” on oral health: a case–control study. *Clin Oral Investig*. 2016;20(3):469-475. doi:10.1007/s00784-015-1527-z
11. Shetty V, Harrell L, Clague J, Murphy DA, Dye BA, Belin TR. Methamphetamine Users Have Increased Dental Disease: A Propensity Score Analysis. *J Dent Res*. 2016;95(7):814-821. doi:10.1177/0022034516640478
12. Smit DA, Naidoo S. Oral health effects, brushing habits and management of methamphetamine users for the general dental practitioner. *Br Dent J*. 2015;218(9):531-536. doi:10.1038/sj.bdj.2015.341
13. Spolsky VW, Clague J, Murphy DA, et al. Periodontal status of current methamphetamine users. *J Am Dent Assoc*. 2018;149(3):174-183. doi:10.1016/j.adaj.2017.10.017