ASAM American Society of Addiction Medicine

ASAM Clinical Considerations: Medetomidine Intoxication and Withdrawal

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Introduction

Although overdose mortality in the US has recently declined,[1] morbidity associated with unregulated substance use continues to exact a serious toll on individuals and communities. The opioid supply has been shifting rapidly,[2] with exposure to combinations of potent synthetic opioids, sedatives, analgesics, and synthetic precursors leading to new health impacts and medical complexities for patients with substance use disorders (SUDs). Medetomidine, a veterinary sedative that acts as an imidazoline and α2-adrenergic receptor agonist, has recently emerged as an adulterant that is associated with uniquely severe withdrawal syndrome, necessitating rapid adjustment of clinical practice.[2-4]

Medetomidine was first detected in the drug supply in 2021 via testing of seized samples, wastewater, and drug paraphernalia,[5] and has been expanding across US geographical regions. The emergence of medetomidine followed a pattern similar to that of xylazine, and the National Institute of Standards and Technology (NIST) Rapid Drug Analysis and Research (RaDAR) program reported nationwide medetomidine presence in opioid-positive unregulated substance and drug paraphernalia samples reported by December 2025.[4] The greatest prevalence remains in the Northeast and Midwest, with adulteration as high as 90% found in some mid-Atlantic opioid supplies.[4]

Like xylazine, medetomidine is approved by the US Food and Drug Administration (FDA) for veterinary use as an intravenous (IV), short-acting sedative.[6,7] Compared to xylazine, medetomidine is 100- to 200-fold more potent at the α2-adrenergic receptor, and 10 times more selective for the α2 vs α1 adrenergic receptor.[8,9] Medetomidine is a racemic mixture of the enantiomers levomedetomidine and dexmedetomidine.[3] Of these, dexmedetomidine is the active form, and isomeric dexmedetomidine is FDA-approved for human use as an IV sedative in surgical and critical care settings.[9] In the absence of robust evidence on human use of medetomidine, existing understanding of dexmedetomidine effects may be particularly informative. Comparing these compounds can also help clinicians understand the impact of medetomidine exposure: In areas of Pennsylvania with the highest measured concentration of medetomidine in the supply, one bag of unregulated fentanyl-medetomidine could contain an amount of dexmedetomidine that is 100 times higher than a typical loading dose of dexmedetomidine in the ICU.[10,11]

In geographic areas where codetection of medetomidine in the unregulated opioid supply is high, acute intoxication is associated with sedation that is unresponsive to opioid reversal agents. Additionally, a rapidly emerging medetomidine withdrawal syndrome manifests severe symptoms and unpredictable clinical course that is not responsive to standard approaches to withdrawal management of central nervous system depressants.[4,12,13]

Medetomidine intoxication and withdrawal represent distinct clinical syndromes with varying timelines, physiologic mechanisms, and treatment approaches. Persistent sedation accompanied by bradycardia and occasionally hypotension is characteristic of acute toxicity, whereas autonomic hyperactivity developing hours after cessation of substance use may suggest withdrawal.

This Clinical Consideration is based on expert consensus and available evidence to address two key questions on the treatment of medetomidine intoxication and withdrawal:

1. For patients presenting for treatment of medetomidine intoxication, what medical interventions are effective for intoxication management?
2. For patients with moderate to severe medetomidine withdrawal, what medical interventions are effective for withdrawal management?

There is insufficient evidence available on this topic to support a clinical practice guideline, and, as such, this document follows the American Society of Addiction Medicine's (ASAM) methodology for clinical considerations. The key questions and their narrative responses focus on current clinical challenges, summarize literature to date, and conclude with clinical consideration statements. It should be noted that the majority of existing evidence on this topic has been generated in hospital settings, so the consideration statements are most relevant for inpatient care. Additionally, the scope of this document will focus tightly on medetomidine intoxication and withdrawal and will not reiterate established best practices for treating opioid use disorder (OUD) and other related conditions. Clinicians should refer to established guidance, such as ASAM's *National Practice Guidelines for the Treatment of Opioid Use Disorder and Clinical Considerations for Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-Potency Synthetic Opioids*[14] for information on evidence-based recommendations on OUD treatment.

Methods

ASAM's Quality Improvement Council (QIC) assembled a group of experts in the treatment of medetomidine intoxication and withdrawal to serve on the writing group for this Clinical Consideration. The writing group members were chosen based on their experience, and all consideration statements reflect the consensus of this group. A separate group of experts were chosen as a peer review panel, and their comments were adjudicated and addressed by the writing group.

The writing group also developed the scope and key questions outlined in Appendix A. Disclosure of interest information was collected in accordance with our methodology and the details are available in supplemental materials.

Broadly, key questions address medetomidine intoxication and withdrawal. ASAM's QIC and Board of Directors approved this Clinical Considerations document in October 2026.

Narrative Literature Search

A narrative literature search was performed in PubMed and PsycINFO for English-language papers from inception to April 21, 2026. The structured search yielded 529 studies, of which 46 met inclusion criteria. Given the rapidly evolving nature of this topic, literature published after the narrative search was conducted was included when identified as relevant by the writing committee. See Appendix A for full details on the literature search.

Consideration Statements

The evidence related to management of medetomidine intoxication and withdrawal is limited, with the current literature being primarily descriptive, retrospective, and experiential in nature. As such, the clinical consideration statements in this document are primarily based on the clinical consensus of the expert committee. **Clinical best practices are likely to evolve over time, and new evidence should be carefully considered by clinicians managing this patient population.**

Key Question 1

For patients presenting for treatment of medetomidine intoxication, what medical interventions are effective for intoxication management?

Evidence Summary

Identification of Medetomidine Intoxication

To date, medetomidine intoxication is overwhelmingly observed in combination with unregulated opioids, although occasional cases have also been reported in association with stimulant use.[4] Although medetomidine exposure can be detected in urine via methods such as liquid chromatography–quadrupole time-of-flight (LC-QTOF) mass spectrometry testing,[15] most clinical settings have limited capacity for such testing and, therefore, diagnosis of medetomidine intoxication is clinical rather than laboratory-based.[3] Clinicians may also use information gathered by public health laboratories or patients using medetomidine test strips to test their personal supply to get a better understanding of local or regional prevalence of medetomidine and associated likelihood of patient exposure.

Patients experiencing severe medetomidine intoxication frequently present with sedation and sinus bradycardia.[5,15] Low blood pressure readings are common among patients exposed to medetomidine, with fewer exhibiting clinically relevant hypotension.[16]

Medetomidine Intoxication Management

Patients presenting with suspected medetomidine intoxication should be assessed for respiratory depression. Given the near ubiquitous co-exposure to fentanyl, reversal of opioid-induced respiratory depression (when present) is the most critical intervention; therefore, naloxone should be administered in incremental doses only until respiration is adequately restored.[3] Given their distinct mechanisms of action, naloxone will not reverse the effects of medetomidine, and a patient may remain sedated; therefore, titrating naloxone to reversal of sedation is not an appropriate clinical target.[16]

Although α2-adrenergic receptor antagonists are used to reverse medetomidine sedation in veterinary settings, they are not approved or recommended for human use at this time. Furthermore, in patients with sustained or chronic medetomidine exposure, use of an α2-adrenergic receptor antagonist may precipitate severe and potentially dangerous α2 agonist withdrawal.

Once respiratory status is restored, medetomidine intoxication can then be effectively managed with supportive care in the majority of patients.[3] Although sinus bradycardia with rates as low as 30 to 40 beats per minute (bpm) and associated hypotension can be observed, this usually improves with IV fluids and, less commonly, requires vasopressors.[3] Three to six hours of post-acute observation should be anticipated for resolution of acute medetomidine intoxication in most patients.

Clinical Considerations

- Overdose involving opioids adulterated with medetomidine should be treated like other polysubstance overdoses suspected to involve opioids. Naloxone should be administered until respiration is adequately restored. Clinicians should target improvement in respiratory status rather than reversal of sedation or return to baseline level of consciousness as sedation may persist.

- If sedation persists in a patient with suspected opioid overdose after naloxone, other causes—including etiologies that are not substance-related—should also be considered. Bradycardia may indicate medetomidine exposure. Medetomidine intoxication should be managed with supportive care that preserves respiration, reduces risk of aspiration, and facilitates adequate tissue perfusion.

Maintain a Broad Differential Diagnosis

Both medetomidine intoxication and withdrawal may resemble other common clinical conditions, including sepsis; precipitated opioid withdrawal; other withdrawal syndromes; serotonin syndrome; and primary cardiovascular, neurologic, or psychiatric disorders. Importantly, these other conditions may coexist, and clinicians should maintain a broad differential diagnosis while evaluating and treating patients.

Key Question 2

For patients with moderate to severe medetomidine withdrawal, what medical interventions are effective for withdrawal management?

Evidence Summary

Medetomidine Withdrawal

The symptoms that characterize medetomidine withdrawal (**Figure 1**) were first identified in patients presenting in Philadelphia and Pittsburgh emergency departments in 2024.[15,17] These patients had a history of unregulated opioid use and had severe autonomic hyperactivity, with symptoms including anxiety, tremor, diaphoresis, nausea, vomiting, agitation, and encephalopathy within a few hours of their last substance use. Notably, these symptoms were not mitigated by γ-aminobutyric acid (GABA) agonists (eg, benzodiazepines, phenobarbital), which can be effectively used to address sympathetic overactivation caused by alcohol or benzodiazepine withdrawal, or by the administration of full opioid agonists, which are effective for opioid withdrawal.[15,17] In contrast, dexmedetomidine infusion was found to be highly effective in alleviating these symptoms, including tachycardia and hypertension.[15,17] Xylazine, also an α2-adrenergic receptor agonist, had been ubiquitous in the unregulated supply in these areas of the US for several years, with xylazine detected in 99% of fentanyl samples tested by the Philadelphia Department of Public Health in 2023.[10] Xylazine exposure, however, has not been associated with a rapid and intense withdrawal syndrome with marked vital sign abnormalities. By identifying medetomidine metabolites in urine and successfully treating withdrawal with dexmedetomidine, clinical and public health teams were able to determine medetomidine exposure as the cause of this severe withdrawal syndrome.[15,17]

Figure 1. Clinical Features Associated with Increasing Severity of Medetomidine Withdrawal*

These categories are intended as a conceptual framework to support clinical recognition and disposition planning. Severity thresholds have not been validated, progression may be rapid, and clinical judgment should guide management decisions. Patients may move along this spectrum during course of treatment.

Clinical Features Across the Spectrum of Medetomidine Withdrawal Severity

Not all symptoms will be present in all patients. Clinical manifestations vary; some patients may progress rapidly along the severity spectrum.

Domain	Mild Withdrawal *Clinically stable*		Moderate-to-Severe Withdrawal *Progressive escalation with risk for physiologic instability and/or end-organ dysfunction*
General presentation	Alert, able to participate in evaluation	→	Escalating distress and autonomic activation that may progress to encephalopathy and/or evidence of end-organ dysfunction
Oral Intake	Tolerating oral intake; may have nausea but able to tolerate oral medications with or without antiemetics	→	Vomiting that may progress to persistent or intractable vomiting with impaired tolerance of oral medications
Heart Rate	Mild Tachycardia (HR may be normal or bradycardic in early withdrawal)	→	Progressive tachycardia, potentially exceeding 140 bpm
Blood pressure	Mild hypertension	→	Progressive hypertension that may advance to hypertensive urgency or emergency
Respiratory findings	Normal or mildly increased respiratory rate	→	Tachypnea may be present and may become severe enough to meet SIRS criteria
Neurologic findings	Anxiety, mild tremor, restlessness	→	Progressive neurologic manifestations including severe tremor, marked agitation, encephalopathy, severe muscle contractions, dystonia/opisthotonus, abnormal movements, or PRES
Temperature	Normal	→	Elevated temperature or hyperthermia may be present
Laboratory findings	Often normal	→	Metabolic abnormalities may be present, including hypokalemia, leukocytosis, elevated lactate, metabolic acidosis, and persistent metabolic derangements
Cardiac findings	None	→	QTc prolongation, troponin elevation, myocardial injury, cardiomyopathy, or reduced ejection fraction may be present
Functional status	Symptoms manageable with supportive care and oral medications	→	Requires intensive symptom management, frequent reassessment, and higher-acuity monitoring
Suggested treatment setting	OP or Medically managed intensive outpatient or residential levels of care with nurse monitoring available (i.e., ASAM Criteria Levels 2.7, 3.7)	→	Frequently requires hospitalization and possible ICU management

Increasing withdrawal severity and clinical care needs

*Examples are illustrative only and should not be interpreted as validated diagnostic thresholds.

Generally, patients who exhibit no signs of persistent α2 agonist toxicity or withdrawal in a 6- to 12-hour observation period are less likely to progress to severe withdrawal.[3] It should be emphasized, however, that existing reports cannot support a definitively safe observation period. Identifying which patients will develop severe withdrawal and in what timeframe post-use is an urgent outstanding research question. Similar to risk prediction for severe alcohol withdrawal syndrome, anecdotal evidence suggests that prior episodes of medetomidine withdrawal requiring treatment in the intensive care unit (ICU) increases the risk of recurrent severe withdrawal syndrome. It has not been determined whether this risk is due to habitual use patterns and local opioid supply, variations in patient physiology, or a combination of factors.

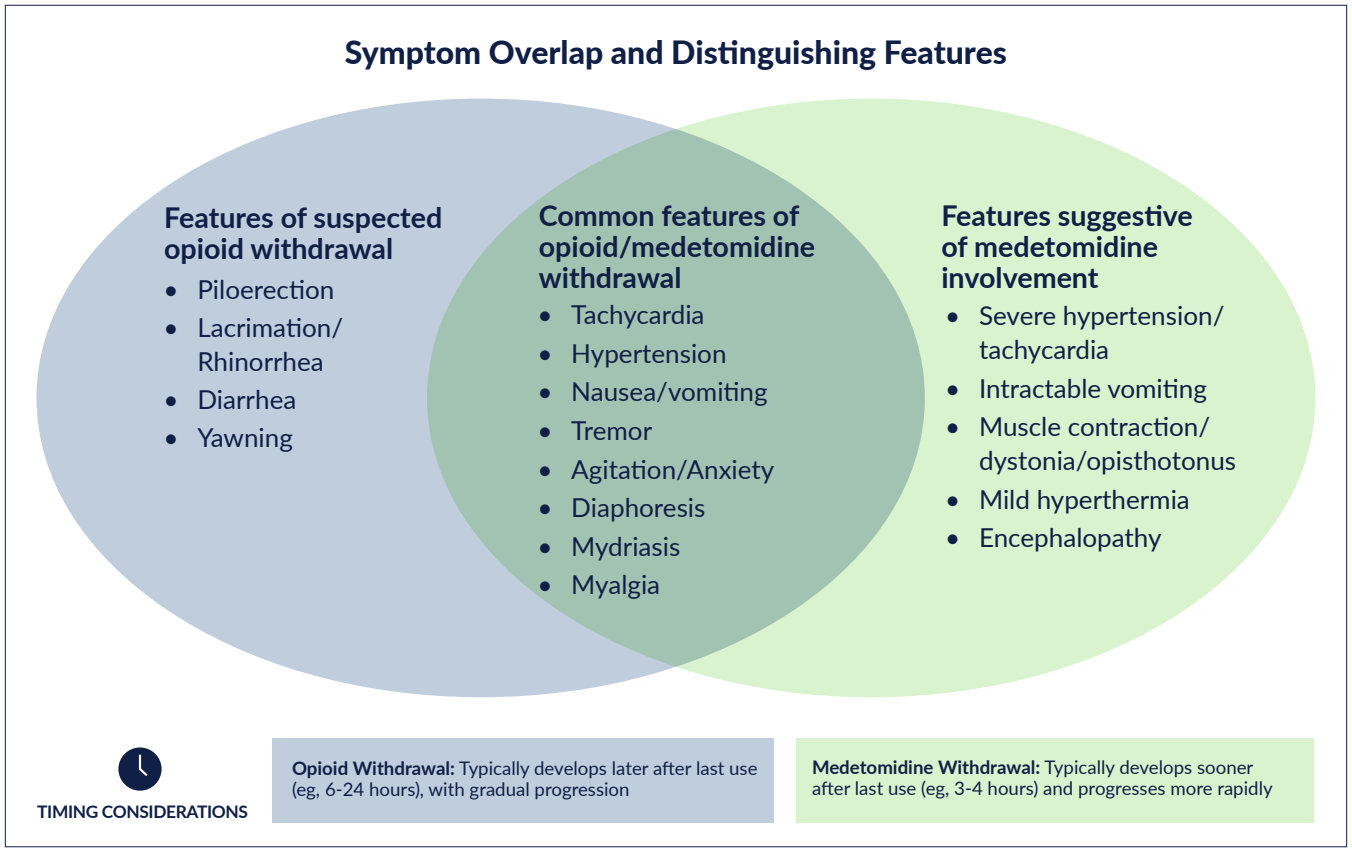
In cases of severe medetomidine withdrawal, symptoms usually begin earlier than those associated with fentanyl alone (**Figure 2**), often within 4 to 6 hours of last unregulated opioid use. Some patients have milder initial symptoms that may progress in severity in the 24 hours following last substance use.[3] Observation of this pattern, however, can be confounded by the effects of ongoing fentanyl–medetomidine use by patients during hospitalization, which may affect the expected timing of withdrawal. Additionally, mild withdrawal symptoms can initially go unrecognized, which may alter the perceived time course.

The autonomic hyperactivity of medetomidine withdrawal syndrome is characterized by hypertension, tachycardia, intractable nausea and vomiting, tachypnea, anxiety, diaphoresis, and tremor without clonus or hyperreactivity (distinct from those associated with other withdrawal syndromes), along with paradoxical lethargy in some patients. Extreme tachycardia (ie, over 170 bpm) and hypertensive urgency or emergency (ie, 170 to 240 mmHg systolic over 120 to 140 mmHg diastolic) have been observed in patients experiencing this syndrome, and some may exhibit encephalopathy and mild hyperthermia.[3,18] Some clinicians

Better understand if a patient may be at risk for moderate to severe medetomidine withdrawal by considering the following:

1. Does the patient have a history of experiencing complicated withdrawal?
2. Is medetomidine present or prevalent in the local supply?
3. Has the patient experienced intoxication with prolonged sedation despite adequate respirations or appropriate opioid reversal?
4. Has the patient checked their drug supply and found it positive for medetomidine (eg, using medetomidine test strips if available)?
5. Does the patient present with sinus bradycardia?
6. Has the patient demonstrated rapid escalation of heart rate and/or blood pressure during your initial observation?

Figure 2. Distinguishing Opioid Withdrawal from Opioid + Medetomidine Withdrawal



have also noted the presence of marked jaw tremor, severe muscle contractions and/or opisthotonus that may be mistaken for seizure, and myoclonus (eg, hiccups). Additional clinical findings can include hypokalemia, metabolic acidosis with elevated lactate, significant leukocytosis, prolonged QTc interval, troponin elevation, acute cardiomyopathy with reduced ejection fraction, and posterior reversible encephalopathy syndrome (PRES).[3,18]

The local drug supply is a key variable when considering whether a patient's symptoms are due to medetomidine withdrawal; the likelihood of severe withdrawal is much greater in areas where medetomidine is prevalent in high concentrations. For this reason, accessible monitoring systems, including drug checking laboratories and public health reporting mechanisms, are necessary to support timely recognition of changing exposure risks and inform clinical practice. An open research question and area of clinical uncertainty is how quickly dependence on medetomidine develops; evidence from patients treated with dexmedetomidine suggests that regular exposure over a matter of days may be sufficient to cause severe withdrawal after abrupt cessation.[19,20]

Medetomidine Withdrawal Management

The closest clinical scenario to medetomidine withdrawal is the iatrogenic dexmedetomidine withdrawal syndrome that has been described in some patients receiving treatment in critical care settings.[20] Observational studies suggest that clonidine and guanfacine may help with weaning such patients from dexmedetomidine.[21,22] Indeed, emerging treatment strategies for medetomidine withdrawal generally rely on the use of α2 agonist medications.[3]

The protocols described in this document were developed in hospital settings, where more severe presentations are encountered (see Appendix B). For example, recent data from the University of Pennsylvania Health System show that among emergency department patients admitted with OUD, 5.7% needed ICU care and dexmedetomidine in the period before high medetomidine prevalence in the supply, [a] while 31.7% needed it after.[23] Similarly, data from the Jefferson Health System show an increase in median quarterly ICU admissions for opioid withdrawal patients from 18, when fentanyl alone dominated the supply, to 64 following the emergence of medetomidine.[24] It is important to note that these findings are based on broad diagnoses of OUD and opioid withdrawal and, therefore, may not capture all patients experiencing medetomidine withdrawal.

Because medetomidine withdrawal does not have a specific diagnostic code and confirmatory testing is not routinely available, the true incidence of medetomidine withdrawal and the proportion of affected patients who require ICU-level care remain unknown. Additionally, these studies do not address the population of patients who may be experiencing mild medetomidine withdrawal who are not admitted to the hospital. However, estimates from an early multicenter study across three hospital systems suggest that ICU admission may be common among patients experiencing severe withdrawal.[25] Milder cases of medetomidine withdrawal may be treatable in residential and outpatient settings.[26]

α2 Agonist Withdrawal

Several α2 agonist medications (eg, clonidine, tizanidine, guanfacine, dexmedetomidine) can be utilized to treat medetomidine withdrawal, and progressive down-titration of these medications allows for a more gradual reduction in α2 receptor activation. Considering these agents' unique pharmacological properties and different routes of administration can be helpful in the treatment of medetomidine

[a] Before medetomidine penetrance (Q1 2020 through Q1 2024) and after medetomidine penetrance (Q2 2024 through Q3 2025), based on community-based drug surveillance.

withdrawal.[3,18] A critical note for clinicians, pharmacists, formularies, and facility or system administrators is that far higher doses of α2 agonist medications than usual are required for withdrawal management of patients regularly exposed to medetomidine. For example, the typical maximum daily dose of clonidine is 1.2 mg/day in divided doses; clinicians treating severe medetomidine withdrawal may titrate much higher daily doses based on clinical response (**Figure 3a; Figure 3b**). Dose escalation should be accompanied by regular monitoring of heart rate, blood pressure, and overall clinical status, with subsequent down-titration as withdrawal symptoms resolve to reduce the risk of hypotension.

Figure 3a. Clinical Management of Medetomidine Intoxication and Withdrawal*

NOTE: The information presented reflects expert consensus and available clinical evidence. It was developed based on care provided in inpatient settings with more severe presentations; milder cases may be treatable with outpatient care.

ACUTE TOXICITY

Common Clinical Findings

- Sinus Bradycardia
- Sedation
- Low blood pressure

INITIAL MANAGEMENT

- Assess for opioid toxicity / decreased respiration/hypoxia
- Administer naloxone if indicated until respiration adequately restored

NOTE: Naloxone reverses opioid toxicity but does **NOT** reverse medetomidine effects; thus patient may remain sedated

Once adequate respirations restored, manage medetomidine toxicity with supportive care

NOTE: Medetomidine testing is unavailable in most clinical settings; diagnosis is based on clinical presentation.

WITHDRAWAL MANAGEMENT

Common Withdrawal Symptoms

- Hypertension/ Tachycardia
- Refractory Emesis
- Anxiety
- Tremor
- Diaphoresis
- Agitation
- Encephalopathy

INITIAL MANAGEMENT

- ✓ Begin oral α2-agonist therapy
- ✓ Treat severe nausea/vomiting
- ✓ Treat opioid withdrawal concurrently

TREATMENT OF SEVERE NAUSEA AND VOMITING

IV or IM D2 receptor antagonist antiemetics may include:

- Olanzapine 5-10mg (PO, IV/IM)
- Droperidol 2.5-5mg IV
- Prochlorperazine 5-10mg (PO/IV)
- Haloperidol 2-5mg (PO/IV)

Additional considerations for all agents:

- May repeat dosing as needed or schedule per standard dosing recommendations
- Monitor for akathisia, dystonia; consider diphenhydramine 25-50mg IV PRN
- Consider ECG monitoring due to QTc prolongation risk

Frequent Monitoring

- ECG to evaluate and monitor QT as indicated by initial findings
- Vital sign monitoring, consider at least q1-2h for at risk patients initially

Symptoms controlled with oral α_2-agonist therapy and antiemetics?

YES

Titrate α2-agonist therapy based on withdrawal symptoms and vital signs (consider dynamic dose adjustment)

Once vital signs normalize and withdrawal symptoms are controlled, gradually down-titrate high-dose α2-agonist therapy over several days

At discharge, consider continued α2-agonist therapy with gradual tapering over weeks and close outpatient follow-up to minimize rebound symptoms and return to use

NO

If vomiting, severe tachycardia, or hypertension persist, initiate IV dexmedetomidine

- Adequate symptom control may require bolus dosing and titration of infusion rate to 2.5 mcg/kg/hr
- Usually required for 24-72 hours

Once oral medications are tolerated:

- Initiate oral and/or transdermal α2-agonist therapy and titrate based on symptoms and vital signs
- Gradually down-titrate dexmedetomidine infusion
- Pause taper for worsening vital signs or withdrawal symptoms
- Consider bolus dosing or return to the previously tolerated infusion rate if severe symptoms recur

CONCURRENT OUD MANAGEMENT

- Symptoms of medetomidine and opioid withdrawal may overlap; medetomidine withdrawal often begins earlier and may elevate COWs scores
  - COWS-driven initiation of full-dose buprenorphine may increase the risk of precipitated withdrawal
- Prioritize full opioid agonist treatment of withdrawal symptoms
- MOUD initiation:
  - Methadone can be initiated and titrated immediately (standard QTc monitoring recommended)
  - Buprenorphine low dose initiation with full opioid agonist bridging is recommended

* Clinical strategies reflect that medetomidine intoxication is most often observed in combination with fentanyl

Figure 3b. Clinical Management of Medetomidine Intoxication and Withdrawal

First Line α_2-Agonist Therapy Options
(**NOTE:** Higher doses than typical may be required for patients with regular exposure)

Oral Clonidine (IR)

Consider for: First-line treatment of alpha-agonist withdrawal. Dynamic PRN dosing based on symptoms, blood pressure, and heart rate; may be used as scheduled therapy with dose titration.

Dosing Range: Severe withdrawal may require an initial loading dose, often administered in divided doses. Doses of 1mg to >1.5 mg given in divided doses over 1-4 hours have been tolerated in select patients.

Subsequent dosing commonly ranges from 0.1-0.3 mg every 2-6 hr. Titration can be considered every 2-4 hr based on symptoms and vital signs.

Clonidine Patch

Consider for: Adjunct to oral clonidine and/or dexmedetomidine; place early in treatment to support transition/de-escalation therapy as it has a delayed onset of action as it reaches steady-state concentrations approximately 2-3 following application.

Dosing Range: 1-2 patches (0.3 mg/day each)

Dexmedetomidine IV Bolus

Consider for: Severe withdrawal; initiation of dexmedetomidine infusion; rapid symptom control during escalation of withdrawal.

Dosing Range: 1 mcg/kg IV; may repeat based on clinical response. Typical cumulative bolus dosing is 1-2 mcg/kg over 1 hr.

Dexmedetomidine Infusion

Consider For: Severe or refractory withdrawal despite oral alpha-agonists and supportive therapy; refractory hypertension, tachycardia, or persistent emesis; hypertensive emergency with end-organ dysfunction.

Dosing Range: Start 0.5-1 mcg/kg/hr; titrate every 20-60 min based on symptoms and hemodynamics, or more rapidly if clinically indicated. Repeat dexmedetomidine boluses while titrating infusion may be considered. Doses up to 2.5 mcg/kg/hr have been reported in severe withdrawal.

Adjunct Oral α_2-Agonist Therapy Options

(Note: Higher doses than typical may be required for patients with regular exposure)

Consider for: Persistent withdrawal symptoms requiring additional control, particularly when clonidine dosing is limited by low blood pressure or heart rate. Provides differing duration of action with less effect on vital signs. Scheduled dosing may be used in combination with symptom-driven clonidine administration.

Guanfacine (IR) Dosing Range: Start 1-2 mg q8-12h; may titrate q8-24h. Doses up to 2 mg q8h have been used.

Tizanidine Dosing Range: Start 2-4 mg q6-8h; may titrate q6-24h. Doses up to 4-8 mg q6-8h have been used. (*Tizanidine has been associated with possibly contributing to torsades de pointes; alternative agents may be preferred in patients with prolonged QTc.*)

NOTE: The information presented reflects expert consensus and available clinical evidence. It was developed based on care provided in inpatient settings with more severe presentations; milder cases may be treatable with outpatient care.

Appendix B provides specific protocols in current use with ongoing refinement. Some approaches utilize the co-administration of multiple α2 agonist medications, while another prioritizes single-agent therapy with oral clonidine before adding other medications. These treatment strategies were developed through clinical experience, and there is no research to date comparing these various approaches. They all prioritize the prompt administration of oral α2 agonist medications as soon as medetomidine withdrawal is recognized and share the frequent reassessment and titration of α2 agonists in response to vital signs and withdrawal symptoms.

Oral clonidine is utilized as the first-line agent for hypertension and tachycardia due to its fast onset of action and additional imidazoline agonist properties. Other agents, such as guanfacine and tizanidine, can be utilized for their differing durations of action and less pronounced effects on heart rate and

blood pressure. In addition to oral medications, some clinicians utilize transdermal clonidine from the outset to assist with eventual tapering. Because transdermal clonidine has a delayed onset of action, clinicians who elect to use patches may apply them early while relying on short-acting α2 agonists for acute symptom control. Some clinicians have also reported administering oral clonidine tablets via the sublingual route when oral intake is impaired, although evidence supporting this practice is limited and clinical experience varies. Intramuscular (IM) or IV bolus dose dexmedetomidine is also being explored as a potential bridge therapy to control initial symptoms and promote tolerance of oral therapies. Use of sublingual dexmedetomidine has been proposed as a potential alternative to parenteral therapies, but there is no published evidence in this population and very limited anecdotal experience. Evaluation of this formulation could inform future treatment approaches.

α2-Adrenergic agonist therapy is the definitive treatment for medetomidine withdrawal syndrome and its associated hyperadrenergic state. Conventional antihypertensive agents may be used as adjunctive therapy, particularly as a bridge while α2-adrenergic agonist doses are titrated or in patients with hypertensive emergency and evidence of end-organ injury. Caution is warranted with β-blockers, especially as monotherapy, in the setting of a hyperadrenergic α2 withdrawal state due to theoretical concerns of unopposed alpha stimulation, although this risk is still debated in the field.[27] If a patient's vomiting is not controlled by combined antiemetic and α2 agonist treatment (see Nausea and Vomiting), or if severe tachycardia, hypertension, agitation, and encephalopathy emerge, treatment with IV dexmedetomidine is recommended. Again, higher than typical doses have been required for patients experiencing medetomidine withdrawal. While the FDA-approved maximium dexmedetomidine infusion rate for ICU sedation is 0.7 µg/kg/h and some intensive care studies have utilized doses up to1.5 µg/kg/h,[28] dexmedetomidine infusion rates of 2.5 µg/kg/h with supplemental bolus dosing as needed have been used to treat severe medetomidine withdrawal, and even higher infusion rates are already being explored.

Because no validated instrument currently exists to assess the severity of this clinical withdrawal syndrome, clinicians should not rely exclusively on any single measure, such as agitation–sedation scales (eg, Richmond Agitation–Sedation Scale [RASS], Riker Sedation–Agitation Scale) or opioid withdrawal scales (eg, Clinical Opiate Withdrawal Scale [COWS]). Although a pediatric α2 agonist withdrawal assessment scale exists,[29] it has not been validated for medetomidine withdrawal syndrome and should not be applied in an adult population. Similarly, vital signs alone may not fully capture the syndrome. Therefore, titration should be guided by a patient's overall clinical presentation (eg, vital signs, autonomic symptoms, patient-reported distress, observed agitation, mental status changes).

In the clinical experience of the expert committee, this approach to dexmedetomidine infusion and titration is well tolerated, even in patients requiring higher infusion rates. Dexmedetomidine is usually required for 24 to 72 hours. When possible, oral medications can be initiated to facilitate weaning of dexmedetomidine. Once dexmedetomidine has been discontinued, a patient can continue withdrawal management with oral α2 agonists with eventual tapering. If a clonidine patch was applied at the outset of treatment, it will have reached therapeutic levels and may assist in this taper.

Adjunctive medications may also be used to improve patient comfort and facilitate treatment while α2 agonist therapy is being initiated or optimized. Although these medications do not directly address the underlying α2-adrenergic withdrawal syndrome, clinicians may utilize agents such as benzodiazepines or phenobarbital for severe anxiety, agitation, or distress, particularly when access to α2 agonist therapy is delayed or symptoms remain uncontrolled during titration. Similarly, antiemetic medications may be required to facilitate oral medication administration (see Nausea and Vomiting). These adjunctive

therapies should generally be viewed as supportive measures rather than definitive treatment of medetomidine withdrawal.

High-dose oral α2 agonist therapy should be down-titrated prior to hospital discharge. When acute withdrawal symptoms are controlled, including normalization of vital signs and tolerance of oral medications, clonidine and other α2 agonists can be down-titrated in a stepwise fashion over the course of days. Once a patient's symptoms are controlled and stabilized on more standard doses of α2 agonists, patients can be considered for discharge to the community. Based on clinical experience, many patients require ongoing α2 agonist therapy at discharge, with slower down-titration over the course of weeks to months. Patients may benefit from close outpatient monitoring for blood pressure and symptoms; at least weekly follow-up with a medical professional would be ideal.[30]

Clinical experience suggests that discontinuing α2 agonist therapy too soon can result in rebound symptoms, including hypertension, anxiety, restlessness, and α2 agonist craving that may contribute to patients' return to use. Additional research is needed to identify the appropriate follow-up care for patients based on their clinical profiles.

Nausea and Vomiting

The severe nausea and vomiting seen in medetomidine withdrawal syndrome—which is often reported to be refractory to serotonergic medication treatment (eg, ondansetron)—may render treatment with oral medications difficult or impossible at first.[3,25,31] Instead, IM or IV D2 receptor antagonists (eg, olanzapine, haloperidol, droperidol, prochlorperazine) have been used, with repeated or scheduled doses often needed. Administration of antiemetics early in treatment is recommended for nausea or vomiting.

If antiemetics are limited by QTc prolongation, treatment with transdermal scopolamine or IM trimethobenzamide can be considered in some cases.[3,17] Limited clinical experience suggests that aprepitant or fosaprepitant may also be effective without direct QTc prolongation. This aggressive approach is required to bring nausea and vomiting under control and facilitate oral dosing with α2 agonists. Due to the risk of QTc prolongation conferred by these medications, electrocardiogram monitoring is recommended.

Underlying OUD

Patients with medetomidine withdrawal syndrome typically have concurrent use of high-potency synthetic opioids and require treatment for concomitant opioid withdrawal. Further, initiation of ongoing FDA-approved medications for OUD (MOUD) remains essential.[14,32] Selection of MOUD should be guided by a patient's individual needs, preferences, treatment goals, and ability to continue treatment after hospitalization. In the context of medetomidine withdrawal, when buprenorphine is the preferred medication for ongoing OUD treatment, a low-dose buprenorphine initiation protocol is recommended. As stated in ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids, low-dose buprenorphine initiation protocols typically include down-titration of full agonist opioids in parallel with up-titration of buprenorphine and can potentially include nonopioid adjunctive agents (eg, ketamine).[14] These protocols can be initiated prior to significant opioid withdrawal onset, as they are intended to mitigate the risks of precipitated withdrawal and can be started in conjunction with medetomidine withdrawal management as tolerated.[3,31]

A low-dose buprenorphine initiation protocol is recommended for treatment of medetomidine withdrawal because symptoms of medetomidine and opioid withdrawal overlap (**Figure 2**); as such, COWS scores may overestimate opioid withdrawal and confound interpretation of buprenorphine readiness. For example, if a COWS score of 13 or higher is recorded within a few hours of a patient's last reported substance use, their clinical presentation should be assessed with the possibility that symptoms are attributable to medetomidine withdrawal, and administration of standard doses of buprenorphine may put the patient at increased risk of precipitated opioid withdrawal.[3] For this reason, full opioid agonist therapy (eg, methadone, oxycodone, hydromorphone) is often used for initial control of opioid withdrawal symptoms.

For patients who prefer and can access methadone treatment for their OUD, methadone can typically be started following standard initiation protocols. If patients experiencing medetomidine withdrawal have initially prolonged QTc, standard work-up and treatment with repeat monitoring are recommended, as QTc may normalize as the medetomidine toxidrome or withdrawal syndrome improves, allowing for the safe initiation of methadone (**Figure 4**).

Figure 4. Potential Pitfalls in the Recognition and Management of Medetomidine Withdrawal

Recognition Pitfalls

Assuming symptoms are opioid withdrawal alone

High COWS scores and severe autonomic symptoms may reflect concurrent medetomidine withdrawal, not opioid withdrawal alone.

Diagnostic anchoring on a single diagnosis

Tachycardia, tachypnea, hyperthermia, leukocytosis, elevated lactate, and altered mental status may reflect medetomidine withdrawal, a co-occurring medical condition, or both. Withdrawal and other diagnoses may coexist.

Assuming mild symptoms will remain mild

Progression from mild to severe withdrawal is difficult to predict and may occur rapidly.

Relying on a single score, symptom, or vital sign

No validated severity instrument exists. Treatment decisions should be based on the overall clinical presentation.

Management Pitfalls

Titrating naloxone to wakefulness

Naloxone should be titrated to restoration of adequate ventilation, not normalization of level of consciousness. Persistent sedation may reflect medetomidine toxicity.

Treating autonomic symptoms with opioids, benzodiazepines, phenobarbital, or antihypertensives alone

These treatments do not adequately address the underlying α2-withdrawal syndrome.

Delaying α2-agonist therapy due to hypoactive state

Hypoactivity with or without encephalopathy does not necessarily indicate adequate control of the underlying α2-withdrawal syndrome. Delayed treatment may allow rapid symptom escalation and loss of oral medication tolerance.

Abrupt discontinuation of α2-agonist therapy

May result in rebound hypertension, anxiety, restlessness, and recurrent withdrawal symptoms.

Key Practice Takeaways

- ✓ Treat **opioid withdrawal and medetomidine withdrawal in parallel**
- ✓ Treat **withdrawal and other potential co-occurring diagnoses in parallel**
- ✓ Maintain a **broad differential diagnosis**
- ✓ Base treatment decisions on the **overall clinical presentation,** not a single score, symptom, or vital sign
- ✓ Reassess frequently; progression from mild to severe withdrawal may be rapid and difficult to predict

Post-Acute Care for Stabilized Patients

For patients whose withdrawal has been stabilized in a hospital setting, transfer to a Level 3.7: Medically Managed Residential Treatment program (per The ASAM Criteria) is appropriate. Such patients may have initiated buprenorphine or methadone and still require clonidine doses that warrant vital sign monitoring and daily assessment by a medical professional. A Level 3.7 program can provide this intensity of service as the clonidine taper proceeds, which is similar to the treatment of patients who are started on a high-dose benzodiazepine taper for benzodiazepine or alcohol withdrawal in a hospital setting and continue this taper at Level 3.7. Information on best practices in care transitions following hospital discharge is detailed in the ASAM Consensus Standards for *Substance Use Disorder Care Capabilities in Hospitals and Emergency Departments*.[33]

Clinical Considerations

- Clinicians should remain informed about local drug supply trends, emerging adulterants, and regional surveillance findings related to medetomidine.
- For patients who use unregulated opioids in areas where medetomidine is present, rapid progression of a severe withdrawal syndrome that is unresponsive to traditional therapies should prompt consideration of medetomidine withdrawal.
- For patients with known medetomidine exposure, early treatment with antiemetics and high doses of α2 agonist medications with frequent reassessment and titration based on vital signs and withdrawal symptoms is suggested **(Figure 2**).
- Patients at risk of medetomidine withdrawal and their caregivers should be provided with guidance to seek emergency department care should intractable vomiting, tremor, agitation, encephalopathy, or vital sign abnormalities emerge.
- IV or IM D_2 receptor antagonists (eg, olanzapine, haloperidol, droperidol, prochlorperazine) are recommended to treat uncontrolled vomiting associated with medetomidine withdrawal.
- IV treatment with dexmedetomidine is recommended when a patient with medetomidine withdrawal is experiencing the following:
  - Vomiting that is not controlled by combined antiemetic and α2 agonist treatment
  - Severe tachycardia, hypertension, agitation, and encephalopathy emerge despite treatment
- Given the ubiquity of opioid exposure in patients experiencing medetomidine withdrawal, adequate treatment of concurrent opioid withdrawal is typically required. Patients can begin MOUD treatment in conjunction with acute medetomidine withdrawal management.
- Selection of clinical tests and frequency of medical monitoring for patients experiencing medetomidine withdrawal should be individualized, based on initial clinical findings, patient symptoms, and changes in clinical condition, as well as clinician judgment.
  - Suspected or confirmed medetomidine withdrawal should not preclude a comprehensive, standard medical evaluation guided by the patient's presenting symptoms. Regular assessment of vital signs is critical.
  - Continuous monitoring, including telemetry and regular assessment of vital signs is critical for patients who require hospital management of medetomidine withdrawal.

Population-Specific Considerations

Risk Reduction and Patient Safety

Treating a patient for medetomidine intoxication and withdrawal is an opportunity to begin treatment for underlying OUD, but it is also an opportunity to help protect a patient's health if they are not yet ready for treatment. For example, clinicians can provide information on medetomidine test strips—including emphasizing that they are not always accurate[34]—and/or direct patients to local drug checking services if they are available. Clinicians can also encourage patients to avoid using substances alone and avoid going through withdrawal alone, as bystanders can help in case of overdose or the need for emergency care. Given the injuries that can occur related to severe sedation, clinicians can also recommend minimizing patient exposure to extreme environmental conditions and external threats whenever possible. Finally, clinicians should provide naloxone to all patients with OUD, with or without medetomidine exposure.

Incarcerated Patients

Due to the frequency of incarceration-induced opioid withdrawal,[35] jails, prisons, and other carceral settings should be aware of the elevated safety risk for people in these settings. Carceral settings should have medetomidine withdrawal recognition protocols, ensure continuation of MOUD and any ongoing α2 agonist medications at intake, and have robust transfer agreements for cases of escalating medetomidine withdrawal.

Pregnant Patients

Patients who are pregnant or have recently given birth should be treated using an individualized risk–benefit approach. Data regarding medetomidine withdrawal in pregnancy are limited; however, clinical experience suggests that the risks associated with severe untreated withdrawal syndrome—including marked hypertension, tachycardia, dehydration, and other complications—outweigh any medication-related risks. Therefore, withdrawal should not be undertreated due to pregnancy. Emerging clinical experience from regions with high prevalence of medetomidine exposure suggests that withdrawal symptoms may develop more rapidly in some pregnant patients.

Treatment approaches are generally similar to those described elsewhere in this document, although closer maternal and fetal monitoring may be warranted. The α2 agonists clonidine, guanfacine, and dexmedetomidine and the D_2 antagonists olanzapine and prochlorperazine are often preferred due to more robust observational safety data in pregnancy when used for other indications.[36-39] Some centers have reported earlier use of dexmedetomidine infusions in severe cases, particularly when withdrawal is accompanied by marked hypertension, tachycardia, or concern for preeclampsia, followed by transition to oral and/or transdermal α2 agonists as symptoms stabilize. Concurrent use of standard obstetric antihypertensive therapies may still be required during initial stabilization as α2 agonists are titrated. Some clinicians have reported using more conservative lower limits for maternal blood pressure and heart rate during treatment in an effort to avoid excessive maternal hypotension and potential fetal effects.

If a pregnant or recently postpartum patient is hypertensive, laboratory testing for markers of preeclampsia and other hypertensive disorders of pregnancy should be conducted. However, clinicians should be aware that medetomidine withdrawal can mimic preeclampsia, and α2 agonist therapy may still be necessary when withdrawal is a significant contributor to the clinical presentation.

Obstetric consultation should be obtained when available. For severe presentations, early involvement of maternal-fetal medicine, obstetric anesthesia, critical care, and neonatal specialists may be beneficial.

Fetal assessment and monitoring should be considered as appropriate for gestational age and clinical status, particularly in patients with clinically significant withdrawal. Patients with a pregnancy at a viable gestational age should ideally receive care in settings with obstetric services and appropriate fetal monitoring capabilities.

Neonates Exposed to Medetomidine

Complicated withdrawal can occur in neonates with opioid and medetomidine exposure, and presentations may differ from those typically observed with opioid exposure alone. Thus, obstetric and pediatric specialists should be aware of this possibility and consider appropriate monitoring of substance-exposed newborns, particularly in regions where medetomidine is prevalent in the drug supply. In addition to following recommended protocols for neonatal opioid withdrawal syndrome (NOWS), consider close monitoring of vital signs and oral tolerance.

Data regarding treatment and monitoring for neonates exposed to medetomidine are limited and represent a needed area of further study. Some experience suggests that neonates exposed to maternal use of medetomidine-adulterated fentanyl may be at higher risk of medetomidine withdrawal when the last maternal use was close to delivery.[40]

For treatment of medetomidine withdrawal in neonates, early dexmedetomidine infusions may be considered given the ability to rapidly titrate dose combined with neonatology experience with dexmedetomidine infusions as a sedative agent in neonatal intensive care units (NICU). Clonidine has been well tolerated in studies of NOWS as an adjunct to opioid therapy[41] and can be considered for primary treatment of medetomidine withdrawal. Close observation of vital signs and respiratory status in a neonatal intensive care unit is recommended during treatment.

Standard observation periods for NOWS are likely appropriate for medetomidine withdrawal, given its half-life is shorter than that for opioids. A study of dexmedetomidine in NICUs showed delayed clearance in preterm infants, which may be considered in determining an appropriate observation period for medetomidine withdrawal symptoms. However, data on clinical presentation, monitoring, and management of medetomidine withdrawal in neonates are extremely limited, highlighting the need for dedicated research to inform future guidance.

Adolescent Patients

Evidence to date does not address how best practices for the treatment of medetomidine withdrawal may differ for adolescents. Given the severity of medetomidine withdrawal syndrome, the principles described here for adult populations are reasonable to apply. These include prioritizing simultaneous treatment of medetomidine withdrawal with α2 agonist medications and opioid withdrawal with full opioid agonists, initiating MOUD, maintaining a broad differential diagnosis, and frequently reassessing the overall clinical presentation due to the potential for rapid progression to more severe withdrawal. Further research is needed on the clinical course and most effective treatment, post-acute withdrawal care, and follow-up strategies for adolescents experiencing medetomidine withdrawal.

Outpatient and Residential Management of Medetomidine Withdrawal

As the evidence stands, there is currently no reliable way to predict the course of medetomidine withdrawal. For this reason, a setting with nurse monitoring available (eg, *The ASAM Criteria* Level 2.7: Medically Managed Intensive Outpatient Treatment, Level 3.7: Medically Managed Residential

Treatment, or Level 4: Inpatient Treatment) may be best equipped to monitor for changes in status and ensure that escalation of symptoms is recognized and addressed. All these levels of care should be able to manage medetomidine withdrawal in patients whose withdrawal symptoms are adequately controlled with oral medications and have not escalated over the past 12 or more hours. More research is needed, particularly regarding whether management of more mild presentations of medetomidine withdrawal can be safely handled in medically managed outpatient settings without nurse monitoring (ie, *The ASAM Criteria* Level 1.7: Medically Managed Outpatient Treatment).

Evidence regarding outpatient and residential management of medetomidine withdrawal remains limited, and the majority of published clinical documentation is derived from inpatient settings. Although some patients with mild withdrawal symptoms may be successfully managed in medically managed outpatient and residential settings, it remains difficult to predict which patients will experience severe withdrawal. Thus, outpatient and residential treatment should be approached cautiously, with close follow-up and escalation to emergency department or hospital-based evaluation and intervention as needed. Clinicians and patients should understand that, like alcohol and benzodiazepine withdrawal, medetomidine withdrawal can be life-threatening to the point of requiring critical care transport.

Most of the oral medications that are in use for inpatient treatment of medetomidine withdrawal can be provided in medically managed outpatient and residential settings. If a patient tolerates oral dosing and their vital signs are not severely abnormal, adequate control of milder withdrawal symptoms can be addressed without hospitalization.[30] Some patients may require higher doses of oral α2 agonists. In these cases, escalation beyond standard doses in outpatient and residential settings should be individualized based on prescriber experience and insurance medication coverage, as well as a patient's ability to monitor blood pressure at home and engage in close follow-up. Patients with severe vomiting, inability to tolerate oral medications, markedly abnormal blood pressure or heart rate, altered mental status, rapidly progressive symptoms, high-risk medical comorbidities (eg, congestive heart failure, cardiomyopathy), or a history of severe medetomidine withdrawal requiring hospitalization or ICU-level care should be referred for emergency department evaluation or hospital-based management. Because progression from mild to severe withdrawal may be difficult to predict, clinicians should provide patients receiving outpatient care with clear instructions regarding symptoms that warrant urgent reassessment.

Clinical experience suggests that outpatient and residential management is more successful when concurrent OUD is addressed, including initiation or continuation of MOUD when appropriate. Some clinicians have also found that initiating α2 agonist therapy before the onset of severe withdrawal symptoms may help mitigate rapid symptom escalation in patients planning to reduce or discontinue use. Complete abstinence from unregulated substances may not be a patient's goal, so clinicians should support plans for gradual reduction in use.

An additional approach to outpatient management has been developed in settings with high prevalence of medetomidine adulteration, where opioid and medetomidine withdrawal are addressed sequentially. This approach first addresses establishing the patient on MOUD (eg, methadone at an opioid treatment program [OTP], buprenorphine in a clinic setting), even before the cessation of unregulated substance use. After the patient is started on MOUD, α2 agonist withdrawal from the cessation of substance use is addressed through the approaches outlined in this Clinical Consideration document as MOUD continues to be titrated (see Underlying OUD).[30]

Home blood pressure monitoring may be helpful when feasible. Some clinicians also utilize transdermal

clonidine in outpatient settings to provide baseline α2 agonist coverage, recognizing that patches have a delayed onset of effect and may require concurrent short-acting oral therapy during initiation. Some clinicians have also reported using longer-acting α2 agonists such as guanfacine during outpatient tapering; however, comparative data regarding outpatient α2 agonist management is unavailable, representing a needed area of further study.

Close follow-up is recommended, with visit frequency individualized based on symptom severity, patient stability, and available resources. Follow-up should include assessment of vital signs, withdrawal symptoms, medication adherence, ongoing exposure to unregulated opioids, continuity of MOUD treatment, and symptoms of excess α2 agonism (eg, dizziness, syncope, excessive sedation).

When prescribing α2 agonist medications, clinicians should consider a patient's anticipated ability to engage in follow-up care and safely manage their medications. Taper plans should be individualized and developed using a risk mitigation approach. For patient populations in which follow-up may be inconsistent (eg, patients who are unhoused), simpler or more accelerated taper strategies may be more feasible. Ensuring their α2 agonist medications are dispensed in the same interval as their MOUD could also be helpful. Patients should receive counseling regarding how prescribed α2 agonist medications should be managed if return to use occurs, given concomitant exposure to prescribed α2 agonists and unregulated opioids containing medetomidine may increase risk of excessive α2-adrenergic effects.

Resource availability varies substantially across communities and healthcare systems. Clinicians practicing in settings without local addiction medicine, toxicology, intensive care, or other specialty resources may encounter challenges in managing severe medetomidine withdrawal. Facilities should consider developing local protocols and escalation pathways for consultation, transfer, and more intensive levels of care when local resources are insufficient to safely manage severe presentations. Appropriate pathways will vary based on local capabilities and available regional resources.

Conclusions

Medetomidine withdrawal is an emerging clinical concern that reflects the rapidly changing nature of the unregulated opioid supply. This withdrawal syndrome has a more rapid onset and more severe symptom presentation than is seen in withdrawal from other substances, and clinicians have had to develop new treatment protocols. Medetomidine withdrawal can be life-threatening and requires critical care management more often than opioid withdrawal without this adulterant. This document reflects current clinical consensus, which will likely continue to evolve.

Even as clinicians determine how to treat patients experiencing medetomidine withdrawal, they do not have all the tools they need. As medetomidine spreads in the drug supply, it is crucial for clinicians, treatment facilities, and healthcare systems to understand the composition of the local drug supply to determine if medetomidine withdrawal is likely to be present. Therefore, effective drug supply monitoring and information dissemination are essential, and lack of medetomidine testing is an impediment to care. Rapid point-of-care testing for medetomidine metabolites would help clinicians better target effective care approaches.

In regions where medetomidine is prevalent in the drug supply, the healthcare and SUD treatment systems have been challenged in new ways. Rapid innovation is urgently needed to match the pace of change in the unregulated opioid supply, from potentially evaluating and repurposing medications approved for other indications, to developing specialized intermediate care units, to implementing consistent diagnostic

coding, to using billing models that reimburse for the complex care needed to effectively manage patients experiencing medetomidine withdrawal. While research comparing treatment approaches is needed, dissemination of current best practices, community and provider education, and improved communication between behavioral health settings and medical centers are immediate tools to improve patient outcomes. This withdrawal syndrome is a key example for which a public health approach that brings together surveillance testing, epidemiology, and clinical innovation is required.

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Appendix A—Literature Search Methodology

Table A.1. Medetomidine Clinical Considerations: Scope and Key Questions

Population	Patients with medetomidine exposure, including pregnant and peripartum patients
Intervention	Interventions to treat medetomidine intoxication Interventions to treat medetomidine withdrawal
Comparator	TAU or other
Outcomes	Mortality Morbidity Substance use Initiation, engagement, or retention in treatment Precipitated withdrawal Bradycardia Hypotension Opioid toxicity Withdrawal severity Complications of withdrawal syndrome (eg, cardiac, neurological)
Timing	Any
Setting	Any healthcare setting (eg, hospital, ICU, ED, specialty SUD, street medicine, EMS, crisis response centers, The ASAM Criteria Levels 3.7 and 4, other medical specialty providers [addiction medicine providers, CJ settings])
Key Questions	1. For patients presenting for treatment of medetomidine intoxication, what medical interventions are effective for intoxication management? 2. For patients with moderate to severe medetomidine withdrawal, what medical interventions are effective for withdrawal management?

The following databases were searched during April 2026: PsycINFO and PubMed. The search was very broad to allow any peer-reviewed article published in English (from inception to April 21, 2026). Articles were reviewed, and hand searching for included publications was also completed. We identified 542 records and included 44 (**Figure A.1**).

Inclusion Criteria: Peer-reviewed publications of various designs that include the topic of the review as a primary focus.

Exclusion Criteria: No abstract or abstract only (without full text); the following publication types: dissertation/thesis, conference proceedings, commentaries, or editorials; systematic reviews that have subsequently been updated (updated version will be included); and not available in English.

PubMed Lit Search String (n= 497): (("medetomidine"[Supplementary Concept] OR "medetomidine"[All Fields] OR "medetomidine"[MeSH Terms] OR ("dexmedetomidine"[Supplementary Concept] OR "dexmedetomidine"[All Fields] OR "dexmedetomidine"[MeSH Terms] OR "dexmedetomidine s"[All Fields])) AND ("withdraw"[All Fields] OR "withdrawal"[All Fields] OR "withdrawals"[All Fields] OR "withdrawing"[All Fields] OR "withdraws"[All Fields] OR "intox*"[All Fields])) AND (english[Filter])

PsycINFO Lit Search String (n = 40): (medetomidine OR dexmedetomidine) AND (withdrawal or intox*)

Figure A.1. PRISMA Chart

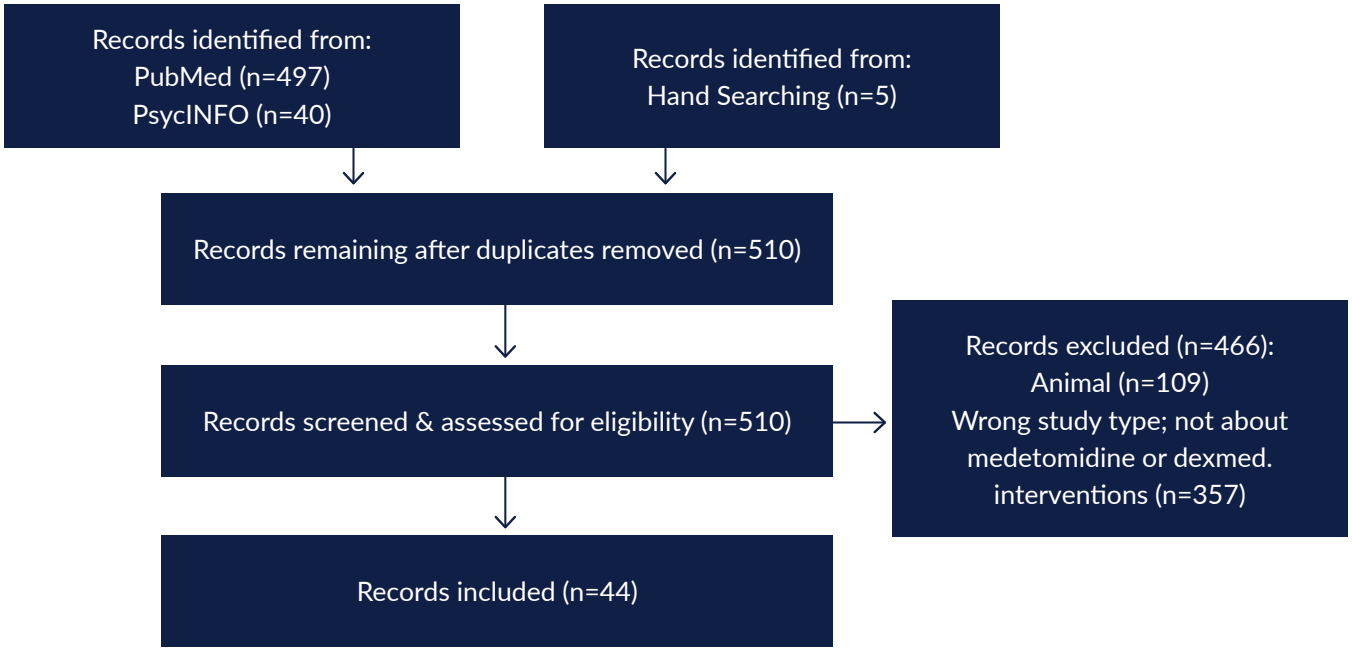


Table A.2. List of Included Studies

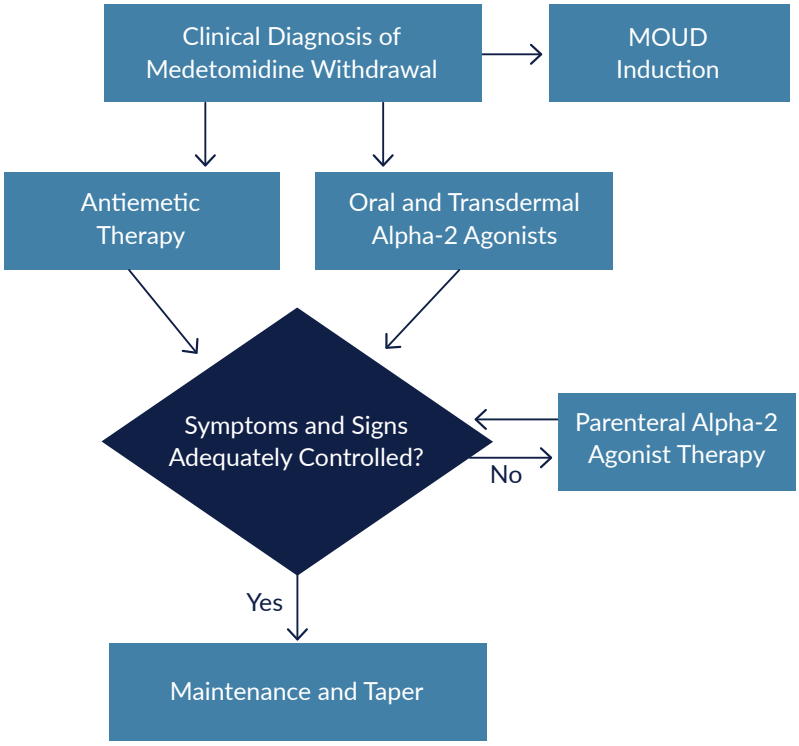
Author	Title
Angles 2026	Emergence of Medetomidine in New York's Illicit Drug Supply
Acharya 2026	Dexmedetomidine-Associated Polyuria Mimicking Diabetes Insipidus
Basappa 2026	Evaluation of Clonidine Utilization for Dexmedetomidine Discontinuation in the Intensive Care Unit
Lynch 2026	Emergence of Medetomidine in the Illicit Drug Supply: Implications for Emergency Care and Withdrawal Management
Hull 2025	A Case of Maternal and Neonatal Withdrawal After Exposure to Fentanyl Adulterated With Medetomidine
Phillips 2025	Evaluation of Institution-Specific Strategy for Converting Dexmedetomidine to Clonidine in a Pediatric Cardiac Intensive Care Unit
Huo 2025	The Shifting Landscape of a Fentanyl Adulterant: Moving From Xylazine to Medetomidine
London 2025	Severe Fentanyl Withdrawal Associated With Medetomidine Adulteration: A Multicenter Study From Philadelphia, PA
Durney 2025	Biochemical Identification and Clinical Description of Medetomidine Exposure in People Who Use Fentanyl in Philadelphia, PA
Johnson 2025	Diagnosis and Management of Medetomidine Withdrawal: Clinical Implications of the Shifting Illicit Opioid Landscape
Ostrowski 2025	Notes from the Field: Severe Medetomidine Withdrawal Syndrome in Patients Using Illegally Manufactured Opioids - Pittsburgh, Pennsylvania, October 2024-March 2025
Huo 2025	Notes from the Field: Suspected Medetomidine Withdrawal Syndrome Among Fentanyl-Exposed Patients - Philadelphia, Pennsylvania, September 2024-January 2025
Nayani 2025	Medetomidine-Associated Opioid Overdoses in Chicago, Illinois: A Report of 3 Cases
Lee 2025	Guanfacine Use in the ICU for Management of Sedation Weaning
Kim 2024	Evaluation of Dexmedetomidine Withdrawal and Management After Prolonged Infusion
Stroeder 2024	Identification of a Conversion Factor for Dexmedetomidine to Clonidine Transitions
Lakra 2023	Dexmedetomidine Withdrawal Mimicking ST-Elevation Myocardial Infarction
Knapp 2023	Dexmedetomidine Withdrawal Syndrome in Children in the PICU: Systematic Review and Meta-Analysis
Rajendraprasad 2023	Clonidine use during dexmedetomidine weaning: A systematic review

Author	Title
Soloduik 2022	Weaning Dexmedetomidine in Non-ICU Areas: An Implementation Effort
Nguyen 2021	Clonidine for the Treatment of Agitation After Dexmedetomidine Discontinuation in Pediatric Patients: A Retrospective Cohort Study
Crabtree 2021	Evaluation of an Enteral Clonidine Taper following Prolonged Dexmedetomidine Exposure in Critically Ill Children
Freguson 2020	Dexmedetomidine withdrawal syndrome and opioid sensitivity
Pathan 2020	Evaluation of dexmedetomidine withdrawal in critically ill adults
Bhatt 2020	Effects of a Clonidine Taper on Dexmedetomidine Use and Withdrawal in Adult Critically Ill Patients-A Pilot Study
Salah 2020	Identification of risk factors for hypertension and tachycardia upon dexmedetomidine discontinuation
Liu 2020	The Impact of a Clonidine Transition Protocol on Dexmedetomidine Withdrawal in Critically Ill Pediatric Patients
Bouajram 2020	Incidence of Dexmedetomidine Withdrawal in Adult Critically Ill Patients: A Pilot Study
Glaess 2020	Clonidine as a strategy for discontinuing dexmedetomidine sedation in critically ill patients: A narrative review
Lee 2020	Evaluating the Transition From Dexmedetomidine to Clonidine for the Prevention of Withdrawal in Critically Ill Pediatric Patients
Mohamed 2018	Effectiveness of Clonidine in Treating Dexmedetomidine Withdrawal in a Patient with Co-Existing Psychiatric Illness: A Case Report
Haenecour 2018	Prolonged Dexmedetomidine Infusion and Drug Withdrawal In Critically Ill Children
Brouillette 2015	Posterior Reversible Encephalopathy Syndrome as a Result of Withdrawal from Prolonged Dexmedetomidine
Lardieri 2015	Effects of Clonidine on Withdrawal From Long-term Dexmedetomidine in the Pediatric Patient
Gangnon 2015	Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study
Kukoyi 2012	Two cases of acute dexmedetomidine withdrawal syndrome following prolonged infusion in the intensive care unit: Report of cases and review of the literature
Darnell 2010	Withdrawal from multiple sedative agent therapy in an infant: is dexmedetomidine the cause or the cure?
Miller 2010	Neurologic withdrawal symptoms following abrupt discontinuation of a prolonged dexmedetomidine infusion in a child
Weber 2007	Acute discontinuation syndrome from dexmedetomidine after protracted use in a pediatric patient
Sood 2025	Rise of illicit medetomidine use: A worrisome trend
Sibley 2025	Emergence of Medetomidine in the Unregulated Drug Supply and Its Association With Hallucinogenic Effects
Zhu 2025	Temporal and spatial patterns of xylazine and medetomidine detected in the DEA's National Forensic Laboratory Information System (NFLIS) reports
Crews 2025	Recent advances in the identification and quantification of xylazine and medetomidine in biological specimens
de Andrade Horn 2024	Classics in Chemical Neuroscience: Medetomidine

Appendix B—Sample Medetomidine Withdrawal Protocols

Sample protocols are examples that were in use as of November 2026.

Figure B.1. Medetomidine withdrawal treatment protocol used by the University of Pittsburgh Medical Center



Medetomidine withdrawal:
- Onset within hours of last illicit substance use
- Nausea and vomiting
- Tremor, myoclonic jerks, anxiety, diaphoresis
- Tachycardia and hypertension
- Encephalopathy
- Minimal or no response to GABA and opioid agonists

Antiemetic therapy:
- Ondansetron rarely effective
- Prochlorperazine 10mg IV/IM/PO repeat as needed
- Droperidol 2.5-5mg IV/IM, repeat as needed
- Olanzapine 5-10mg IV/IM, repeat as needed

Oral and Transdermal Alpha-2 Agonists:
- Clonidine 0.3mg PO; repeat up to 2 additional doses in hour 1 as loading dose (total of 0.9mg)
- Transdermal clonidine 0.3mg weekly
- Guanfacine 2mg PO q8 hours
- Clonidine 0.2-0.3mg PO q2 hours for COWS of >5 or >15, respectively
- Tizanidine 2mg PO q8 hours can be considered
- Benzodiazepiness/barbiturates for additional sedation if needed

Parenteral Alpha-2 Agonist Therapy:
- Dexmedetomidine
  - 1 mcg/kg IV bolus
  - 0.5-1.5 mcg/kg/hr IV infusion titrated to Riker 3-4 or RASS - 1-0 (or sedation if scores not recorded)
  - For severe cases: up to 2.4 mcg/kg/hr
- IV Dexmedetomidine can typically be weaned with overlapping oral regimen over 24-72 hours
- Benzodiazepines/barbiturates or ketamine for agitation uncontrolled with dexmedetomidine if needed

Maintenance and Taper:
- PO regimen can typically be weaned after 3-5 days:
  - As PRN clonidine needs resolve, wean guanfacine to 2mg PO BID x 1 day, then 1 mg PO TID x 1 day, then 1 mg PO BID x 1 day, and 1mg PO once x 1 day and remove clonidine patch
- Other symptom-triggered medications as needed

Figure. UPMC medetomidine withdrawal treatment approach. MOUD, medications for opioid use disorder.

Figure B.2. University of Pennsylvania AgileMD [ED] Clonidine Loading Dose Protocol

Step 1 - Loading Dose
- Clonidine 0.2mg once now for SBP 110-130 **-OR-**
- Clonidine 0.4mg once now for SBP 131-180 **-OR-**
- Clonidine 0.6mg once now for SBP >180

2h later

Step 2 - Additional Loading Dose
- Clonidine 0.2mg once PRN SBP 131-160 **-OR-**
- Clonidine 0.4mg once PRN SBP >160

4 h after 1st loading dose

Step 3 - Scheduled Dose
- Clonidine 0.2mg q6h for SBP 110-130 **-OR-**
- Clonidine 0.4mg q6h for SBP 131-180 **-OR-**
- Clonidine 0.6mg q6h for SBP >180

Figure B.3. University of Pennyslvania [ED] Pain and Symptomatic Withdrawal

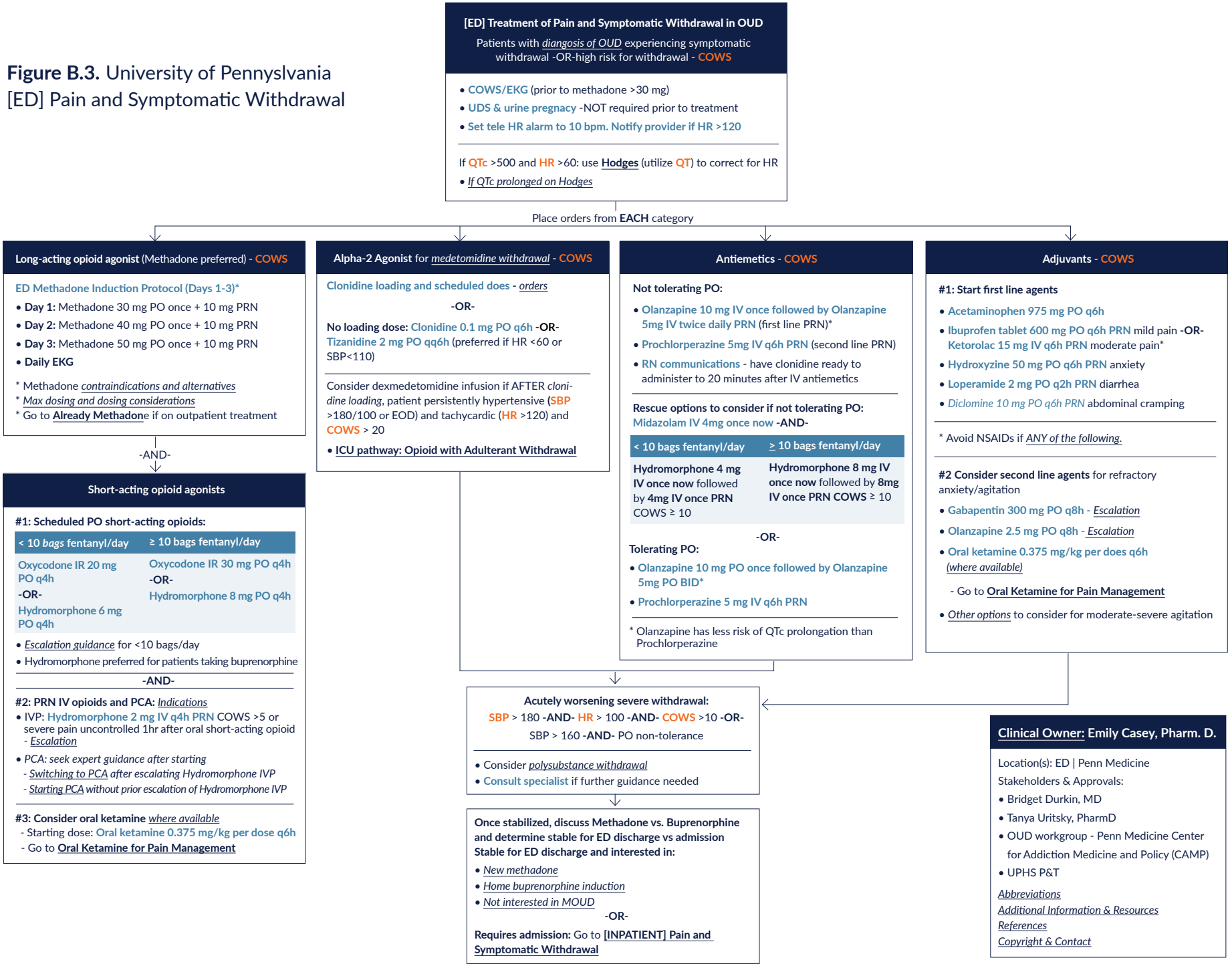


Figure B.4. University of Pennsylvania [Inpatient] Treatment of Pain and Symptomatic Withdrawal in OUD

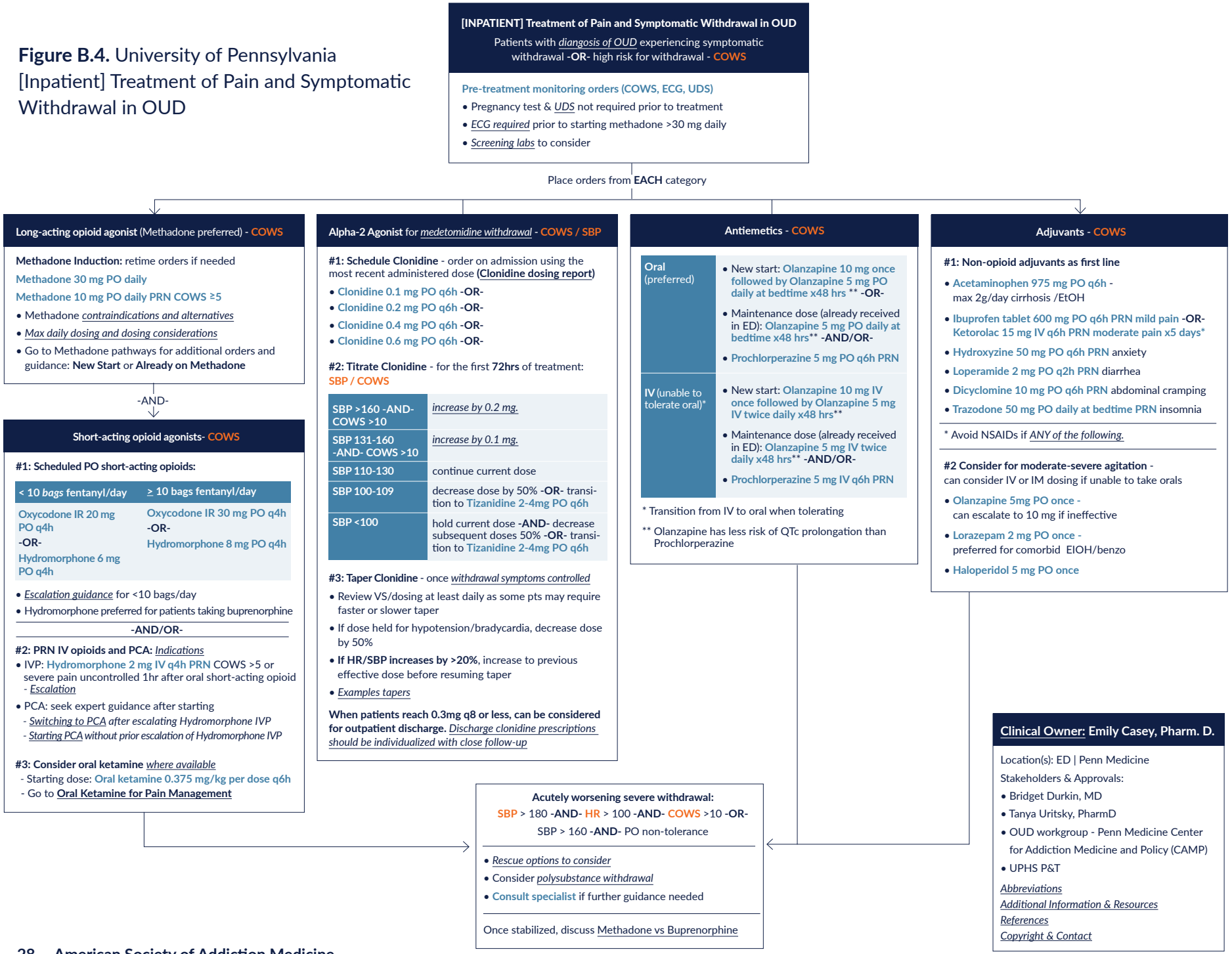


Figure B.5. University of Pennsylvania (ICU) Opioid with Suspected Alpha Agonist (Medetomidine) Withdrawal

[ICU] Opioid with Suspected Alpha Agonist (Medetomidine) Withdrawal - COWS

Inclusion: patients with opioid withdrawal requiring ICU admission due to *severe autonomic dysfunction* accompanied by *other alpha-agonist withdrwal symptoms* **after** adequate *treatment for opioid withdrawal* and maximally tolerated oral therapy following antiemetics for suspected alpha-agonist withdrawal

- Background / regimen for *Xylazine & Medetomidine* withdrwal
- Monitoring orders: *EKG, COWS, sedation scores*
- If QTc >500 and HR >60: use **Hodges** (utilize QT) to *correct for HR*
  - If QTc prolonged on Hodges: check (**BMP, Mg**), replete electrolytes if low (Mg repletion pathway) and repeat **EKG once stat**

Assess for concomitant withdrawal syndromes and treat as needed:

- **Phenobarbital Monotherapy for Moderate and Severe Alchol Withdrawal (ED)**
- **Phenobarbital for Bensodiazepine WIthdrawal**

Order from **EACH** category (unless contraindicated)

Start Dexmedetomidine [BP / HR]

Start Dexmedetomidine:

- RN titrated starting at 0.5 mcg/kg/hr; no more than 0.4mcg/kg/hr q20 min up to 1.5mcg/kg/hr - *titrate to SBP <160*
- Provider driven for doses >1.5 mcg/kg/hr; max 2.5mcg/kg/hr
  - *Typically increase by 0.4mg every 20 min*
  - Consider for sustained SBP>180 or SBP>160 with *severe symptoms* or *signs of organ dysfunction*
- Bolus 0.5mcg/kg at initiation: consider for SBP > 180 or HR >120
  - At discretion of provider or if *rapidly deteriorating* due to suspected medetomidine withdrawal
  - If *bolus tolerated*, increase infusion by 0.5 mcg/kg/hr
  - **Maximum bolus dose:** *total 1mcg/kg in 1 hour*

Contraindications: HR <50, MAP <65, 2nd/3rd degree heart block

Antihypertensives - review BP

- **If severe hypertension persists** despite the use of opioids and dexmedetomidine, treat with short-acting agents per ICU protocol for hypertensive emergency
- **Easily titratable agents:** IV nicardipine drip, IV esmolol drip, IV labetalol, or IV hydralazine

Down-titration of Dexmedetomidine

- *Typically after 24-48h* on stable infusion dose
- Decrease infusion by 0.2mcg/kg every 2 hours
- Pause de-escalation for SBP >160, HR >110 or increased nausea/emesis
- **Patients with suspected primary hypertension:**
  - If isolated SBP >160 without other signs or symptoms of withdrawal, consider higher SBP goal of <180

Clonidine - start when tolerating orals

Start at Clonidine 0.2mg PO q6h

- Increase dose by 0.1mg every 6 hours to facilitate taper off dexmedetomidine if HR >665, SBP >130
  - Some patients may tolerate faster increase by 0.2mg q6h
- **Maximum dose:** 0.6mg q6h; discuss with Addiction Medicine or ICU Clinical Pharmacy Specialist if considering higher dosing

Contraindications (hold parameters): HR <50, SBP <100

Opioids - *start long and short acting opioids* [COWS]

- When patient able, discuss **Medications for Opioid Use Disorder (MOUD)**
- When acute withdrawal is *controlled* and patient tolerating orals, consider starting **Low-dose Buprenorphine Induction**

LONG-ACTING: *Methadone is preferred*. Choose oral **-OR-** *IV*

- EKG once stat (prior to first Methadone dose) and daily if increasing
- Methadone Dosing Report to view doses already administered

	< 10 *bags* fentanyl/day	≥ 10 *bags* fentanyl/day
Oral Methadone (preferred)	Methadone 40mg once + 10mg q4h PRN x2 doses (up to 60mg total day 1 dose) • Increase (while in ICU only) by 10mg daily thereafter for COWS >5 up to 80mg - *orders*	Methadone 40mg once + 10mg q4h PRN x2 doses (up to 60mg total day 1 dose) • Increase (while in ICU only) by 10mg daily thereafter for COWS >5 up to 80mg - *orders*
IV Methadone (if unable to tolerate oral)	IV Methadone 20mg once + 10mg once PRN • May increase by 5mg daily for COWS >5 • Start *oral methadone* as soon as tolerating orals	IV Methadone 20mg once + 10mg once PRN • May increase by 5mg daily for COWS >5 • Start *oral methadone* as soon as tolerating orals

Contraindications: *QTc > 500 via Hodges* or **Child Pugh C**

- *Oxycodone ER / Hydromorphone orders* if Methadone is contraindicated

-AND-

SHORT ACTING: Can be given at same time as methadone. Choose oral **-OR-** IV

	< 10 bags fentanyl/day	≥ 10 bags fentanyl/day
Oral Oxycodone IR (preferred)	Oxycodone IR 30 PO q4h • Increase by 10mg as frequently as q2 hours for COWS >8 • Up to max oxycodone IR *50mg-80mg PO q4h*	Oxycodone IR 40 PO q4h • Increase by 10mg as frequently as q2 hours for COWS >8 • Up to max oxycodone *IR 50mg-80mg PO q4th*
IV Hydromorphone (unable to tolerate oral)	Hydromorphone 2mg IV q3h • Increase by 1-2mg as frequently as q30 minutes for COWS >8 • Up to max hydromorphone *4mg-6mg IV q3h* • Convert to oxycodone when tolerating orals	Hydromorphone 4mg IV q3h • Increase by 1-2mg as frequently as q30 minutes for COWS >8 • Up to max hydromorphone *4mg-6mg IV q3h* • Convert to oxycodone when tolerating orals

- **Hydromorphone 2mg-4mg IV q1h PRN** for rapid symptom control in first 48h
- Order *bowel regimen as needed*. **Go to Acute Constipation pathway.**

Ketamine - consider if uncontrolled pain or severe opioid withdrawal (> 10 bags fentanyl per day)

Ketamine oral solution 0.375 mg/kg per dose q6h

- If unable to tolerate oral, can consider *Ketamine infusion*

Contraindications: recent/active CVA or cardiovascular disease, **Child Pugh** C

Antiemetics

Oral (preferred)	• New start: Olanzapine 10 mg PO once followed by Olanzapine 5mg PO daily at bedtime **-OR-** • Maintenance dose (already received Olanzapine in ED): Olanzapine 5 mg PO daily at bedtime **-AND/OR-**** • Prochlorperazine 5mg PO q6h PRN
IV (unable to tolerate oral)*	• New start: Olanzapine 10 mg IV once followed by Olanzapine 5 mg IV twice daily **-OR-** • Maintenance dose (already received in ED): Olanzapine 5 mg IV twice daily **-AND/OR-**** • Prochlorperazine 5 mg IV q6h PRN

* Transition from IV to oral when tolerating

** Can consider combination of Olanzapine and Prochlorperazine

Contraindication (Olanzapine & Prochlorperazine): *QTc >500 via Hodges*

- EKG once stat for QTc monitoring

Additional Adjunctives

- Order via Opioid Withdrawal order set or **[ED] Pain and Symptomatic Withdrawal / [IP] Pain and Symptomatic Withdrawal** pathways
- *Can consider phenobarbital* if requiring additional sedation. Not routinely indicated, unless patient also reports benzodiazepine or alcohol use

Clinical Owner: Emily Casey, Pharm. D.

Location(s): ED | Penn Medicine

Stakeholders & Approvals:

- Bridget Durkin, MD
- Tanya Uritsky, PharmD
- OUD workgroup - Penn Medicine Center for Addiction Medicine and Policy (CAMP)
- UPHS P&T

Abbreviations
Additional Information & Resources
References
Copyright & Contact

Appendix C—Future Research Directions

Table C.1. Future Research Directions

Knowledge Gap	Key Questions	Research Strategy
Case definition and surveillance of medetomidine withdrawal	• How can medetomidine withdrawal be reliably identified and distinguished from opioid withdrawal and other withdrawal syndromes? • What is the true incidence of medetomidine withdrawal? • What proportion of affected patients require ICU-level care?	• Develop and validate a standardized clinical case definition for medetomidine withdrawal • Assess approaches to incorporating medetomidine withdrawal into diagnostic coding, surveillance, and reporting systems • Conduct epidemiologic studies to estimate incidence, severity, healthcare utilization, and ICU admission rates among patients with medetomidine withdrawal
Natural history, physiologic dependence, and risk prediction	• How quickly does physiological dependence on medetomidine develop? • What is the typical timing and clinical course of medetomidine withdrawal? • What clinical, exposure, or patient characteristics predict progression to severe withdrawal? • Does a history of severe medetomidine withdrawal increase the risk of recurrent severe withdrawal? • What observation period is sufficient to identify patients at risk?	• Conduct prospective observational studies to characterize the course of medetomidine toxicity and withdrawal • Evaluate associations between medetomidine exposure patterns, patient characteristics, and withdrawal severity • Identify clinical factors associated with progression to severe or complicated withdrawal
Drug supply and epidemiology	• How do medetomidine prevalence and concentration in the unregulated drug supply relate to withdrawal risk and severity? • How can drug checking, public health reporting, epidemiology, and clinical information support timely recognition of changing exposure risks and inform clinical practice?	• Investigate methods of linking drug supply, epidemiologic, and clinical data • Evaluate approaches for integrating drug-checking and public health reporting with clinical response
Withdrawal Assessment	• Which clinical features of medetomidine withdrawal should be incorporated into a validated withdrawal severity instrument?	• Develop and validate a standardized medetomidine withdrawal assessment instrument
Pharmacologic management of medetomidine withdrawal	• Which pharmacologic approaches are safest and most effective? • What are the optimal selection, sequencing, titration, combination, and tapering strategies for α2 agonist medications? • What patient characteristics predict onset of rebound symptoms?	• Conduct comparative trials of existing α2 agonist treatment approaches • Evaluate alternative pharmacologic approaches, formulations, routes, and bridge therapies • Identify appropriate care settings, monitoring strategies, duration of α2 agonist therapy, and follow-up care based on patient clinical profiles
Levels of care and models of care delivery	• Which patients with mild or controlled withdrawal can be safely managed in outpatient or residential settings? • What clinical course or monitoring findings should guide escalation to emergency or hospital-based care? • What care delivery models may be needed to manage medetomidine withdrawal across settings?	• Evaluate outcomes across inpatient, residential, and outpatient settings • Develop and validate criteria for safe management, monitoring, and escalation across levels of care

Knowledge Gap	Key Questions	Research Strategy
Pregnancy and neonatal exposure/ withdrawal	• What monitoring and treatment approaches are appropriate for pregnant and postpartum patients? • What is the presentation and clinical course of withdrawal among medetomidine-exposed neonates, and how does it differ from opioid exposure alone? • Which medetomidine-exposed infants require enhanced monitoring or treatment, and what exposure factors predict neonatal withdrawal?	• Characterize maternal and neonatal withdrawal and associated outcomes • Evaluate monitoring and treatment approaches in pregnant patients and exposed neonates
Adolescent medetomidine withdrawal	• What is the course of medetomidine withdrawal in adolescents? • What treatment strategies are safest and most effective for adolescents experiencing medetomidine withdrawal?	• Characterize the presentation, clinical course, and outcomes of medetomidine withdrawal in adolescents • Evaluate safety and effectiveness of α2 agonist and opioid withdrawal treatment strategies in adolescents • Identify appropriate post-acute withdrawal and follow-up care approaches