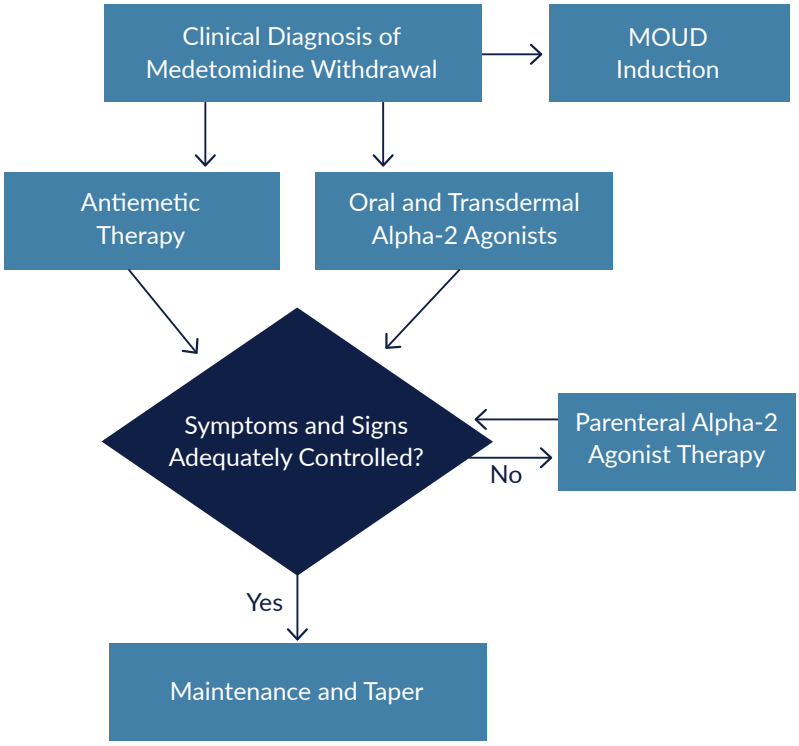
Appendix B—Sample Medetomidine Withdrawal Protocols

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

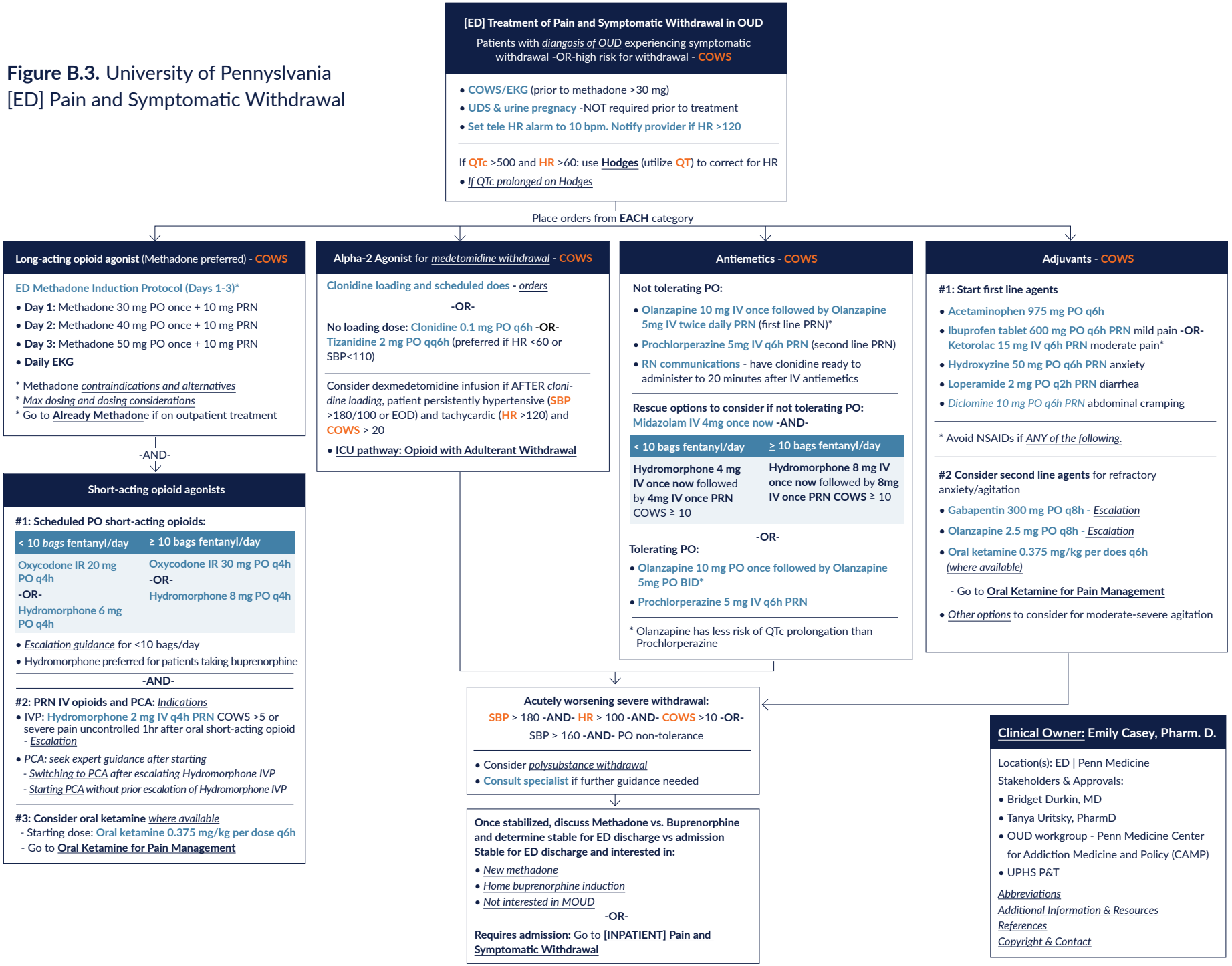


Figure B.4. University of Pennsylvania [Inpatient] Treatment of Pain and Symptomatic Withdrawal in OUD

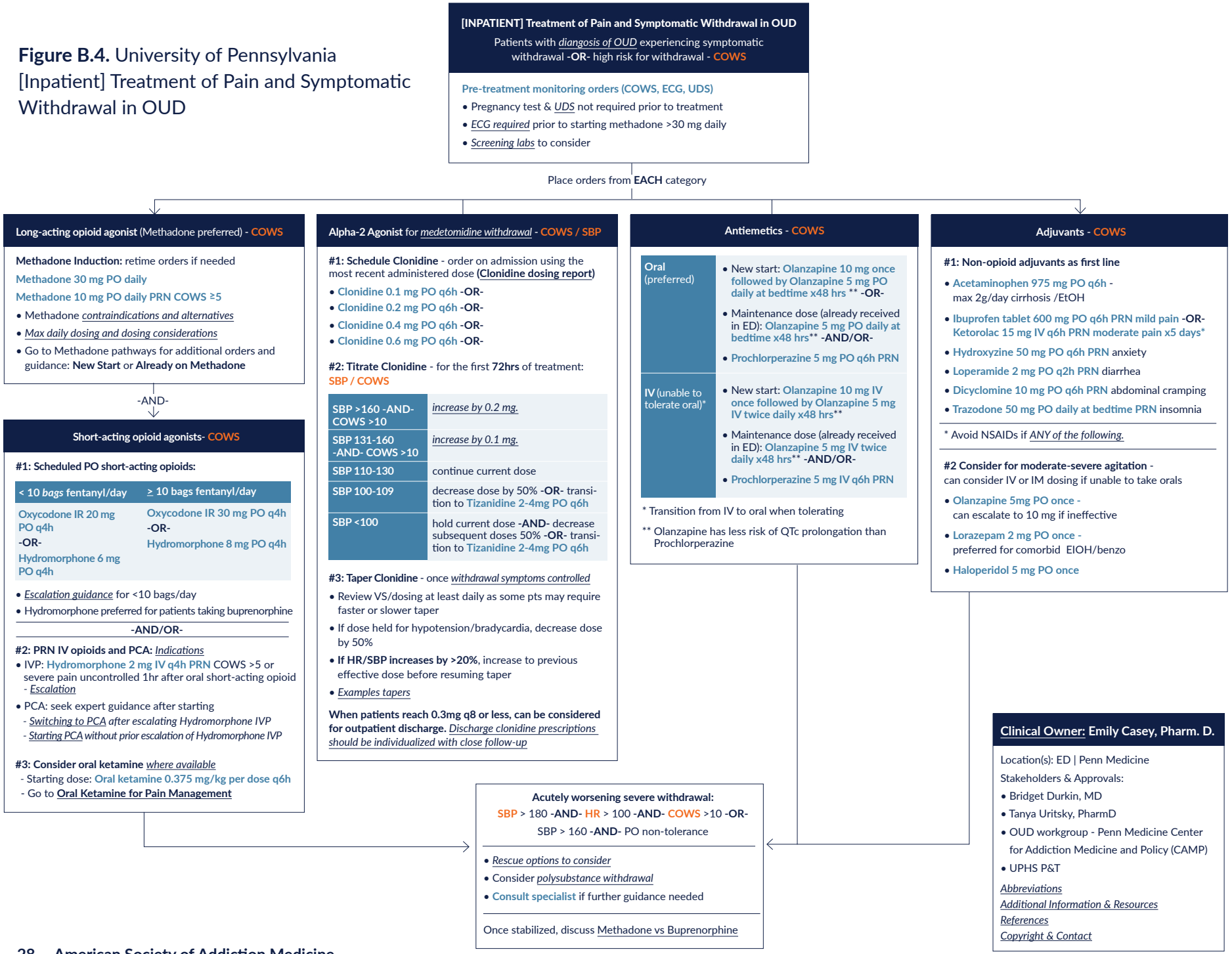


Figure B.5. University of Pennsylvania (ICU) Opioid with Suspected Alpha Agonist (Medetomidine) Withdrawal

[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
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