

UPHS ICU MANAGEMENT: OPIOID WITH SUSPECTED ADULTERANT WITHDRAWAL

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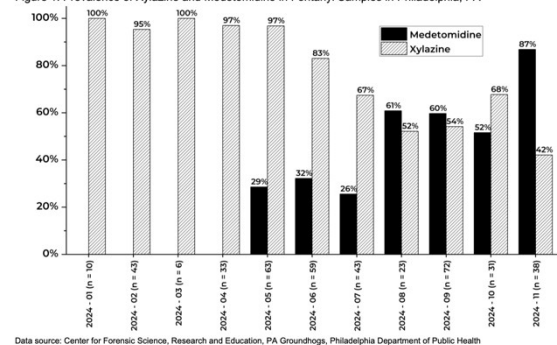
SCOPE OF RECOMMENDATIONS

This guidance pertains to the management of patients reporting illicit opioid (i.e., heroin, fentanyl) use who present with opioid withdrawal and are or will be admitted (from the ED) to the ICU due to the severity of concomitant autonomic symptoms (hypertension, tachycardia, and/or altered mentation) that may be mediated by alpha agonist (adulterant) withdrawal.

Background

The illicit opioid supply in Philadelphia is unregulated and often contaminated with non-opioids, putting patients at risk for complicated withdrawal. Xylazine (“tranq”) and medetomidine are now the most frequently encountered adulterants, and recent trends demonstrate a shift towards medetomidine (figure 1)¹. Due to polysubstance exposure, a multi-modal approach utilizing a backbone of full-agonist opioids to manage withdrawal is recommended. A low threshold to begin α_2 agonist infusion therapy is now recommended.

Figure 1: Prevalence of Xylazine and Medetomidine in Fentanyl Samples in Philadelphia, PA



Data source: Center for Forensic Science, Research and Education, PA Groundhogs, Philadelphia Department of Public Health

Medetomidine

- Used in veterinary sedation/analgesia
- An equal mixture of two enantiomers, dexmedetomidine and levomedetomidine (inactive)
- Highly selective and potent α_2 agonist (100x more than xylazine)²
- Causes bradycardia/hypotension in animals, which is consistent with recent overdose presentations³
- Medetomidine withdrawal has not previously been described, but a distinct syndrome has emerged and appears similar to dexmedetomidine withdrawal syndrome⁴
 - Distinct from xylazine withdrawal, which does not typically present with tachycardia or hypertension and most patients do not require ICU care⁵
 - Cases at Penn have demonstrated severe hypertension (BP >200/100s, hypertensive emergency such as PRES in some cases), tachycardia, delirium, tremors, nausea and/or vomiting

¹ <https://hip.phila.gov/document/4874/PDPH-HAN-00444A-12-10-2024.pdf/>

² PMID: 39405508

³ <https://hip.phila.gov/document/4421/PDPH-HAN-0441A-05-13-24.pdf/>

⁴ PMID: 33227592

⁵ PMID: 38493376

- o Escalating numbers of cases require ICU admission for α_2 agonist infusions +/- anti-hypertensive therapy. Rarely, intubation may be needed. Rebound symptoms occur when medications are tapered too quickly.
- o Risk factors and predictors for severe withdrawal have not yet been defined

Objective

To standardize the care of patients who are or will be admitted to the ICU presenting with opioid withdrawal and autonomic signs and symptoms.

Recommended Medication Regimen

Note: Degree of alertness will influence regimen. Opioid administration should be prioritized.

- (1) Long **and** short-acting opioid
Rationale: High quantities of fentanyl remain prevalent in the illicit opioid supply
- (2) Dexmedetomidine (in lieu of clonidine)
Rationale: Drug checking reports a high prevalence of medetomidine in the illicit opioid supply
- (3) Ketamine
Rationale: Regionally supported (addiction medicine) adjunctive in patients using fentanyl and/or xylazine
- (4) Olanzapine
Rationale: Antiemetic and agitation treatment, may be particularly helpful in patients using xylazine and/or medetomidine
- (5) Antihypertensive agents
Rationale: Severe hypertension may persist despite aggressive treatment with the above therapies. Earlier initiation is warranted if the patient has end organ dysfunction (hypertensive emergency).
- (6) Additional adjunctive medications

(1a) Long-Acting Opioid

- Methadone is the preferred long-acting opioid for all patients regardless of patient desire to be on long term methadone maintenance. Transitioning to a patient's Medication for Opioid Use Disorder (MOUD) of choice (buprenorphine vs methadone) can occur once withdrawal is controlled.
 - o Oral methadone regimen:
 - For patients using < 10 bags per day: 40mg + 10mg x2 doses q4h as needed on day 1 (up to 60 mg)- increase by 10mg daily thereafter for COWS>5
 - For patients using \geq 10 bags per day: Methadone 60mg - increase by 10mg daily thereafter for COWS>5
 - o Unable to tolerate oral therapy or need for rapid control of symptoms (IV Methadone):
 - <10 bags per day: 20mg x 1 + 10mg x 1 (as needed), and then daily
 - If IV continued, may increase by 5mg daily for COWS>5
 - \geq 10 bags per day: 30mg x 1, and then daily
 - If IV continued, may increase by 5mg daily for COWS>5
 - o Use the Hodges formula to calculate QTc if HR > 80 bpm (see "monitoring" below).

- *If methadone contraindicated* (i.e., QTc > 500 mm/sec via Hodges formula, Child Pugh Score C)
 - Oral regimen: Oxycodone ER 40mg PO q8h
 - Increase oxycodone ER dose by 20mg every 4 hours for COWS > 8. Goal COWS ≤ 5.
 - Unable to tolerate PO therapy: Hydromorphone continuous infusion starting at 1mg/hr
 - Provider titrated: increase by 1mg/hr every 1hr for COWs > 8. Goal COWs ≤ 5.

(1b) Short-acting Opioid

- Oral regimen:
 - For patients using < 10 bags per day: Oxycodone IR 30 PO q4h
 - For patients using ≥ 10 bags per day: Oxycodone IR 40mg PO q4h
 - Increase oxycodone IR dose by 10mg as frequently as every 2 hours for COWs > 8. Goal is COWs ≤ 5.
- Unable to tolerate oral therapy: Hydromorphone 4mg IV q2h
 - Increase hydromorphone IV by 1-2mg as frequently as every 30 minutes for COWs > 8. Goal is COWs ≤ 5.

(2) Dexmedetomidine

- Start infusion at **0.5mcg/kg/hr**. Titrated, by nursing, no more than **0.4mcg/kg/hr** every 20 minutes up to 1.5mcg/kg/hr. **Doses > 1.5mcg/kg/hr should be provider driven** to a maximum of 2.5mcg/kg/hr. Titrate to SBP < 160.
- Considerations for dexmedetomidine bolus:
 - A dexmedetomidine bolus of **0.5-1mcg/kg** may be given with initiation at the discretion of the provider OR
 - If the patient is rapidly deteriorating clinically due to suspected medetomidine withdrawal
 - Sustained (>5 min) HR increase of >20% and/or >120 beats/min +/- sustained (>5 min) SBP increase of >20% and/or >180 mmHg
 - With minimal improvement in vital signs, vomiting, and or tremor on dexmedetomidine infusion
 - If bolus dose is tolerated (SBP > 100, HR > 60), increase dexmedetomidine infusion rate by 0.5 mcg/kg/hr
- Contraindications: Heart rate < 50 BPM, MAP < 65 mmHg, Second/Third degree heart block
- De-escalate to clonidine once withdrawal has started to abate and can tolerate oral medications (estimated in 24-48 hours).

(3) Ketamine (Oral/Intravenous)

- Oral: 1.5-3mg/kg divided into q6h dosing
 - Example: 70kg patient would receive 30mg PO q6h
- Unable to tolerate oral therapy: Start infusion at 0.1-0.5mg/kg/hr (maximum initial rate of 50mg/hr, maximum overall rate of 0.5mg/kg/hr). Further dosing instructions can be found in

the subanesthetic Ketamine for Analgesia Guideline.

- Contraindications: Recent/active CVA or cardiovascular disease, Child Pugh C

(4) Olanzapine/Prochlorperazine (Nausea/ Agitation Management)

- Olanzapine IV or PO: 10mg x1, then 5mg daily at bedtime
 - Contraindications: QTc > 500 mm/sec
- Prochlorperazine IV: 10mg q8h (Combination with olanzapine may be considered)
 - Contraindications: QTc > 500 mm/sec

(5) Antihypertensive agents

- If severe hypertension persists despite the use of the above medications, treat with short acting blood pressure lowering agents as per ICU protocol for the management of hypertensive emergency
- Easily titratable agents such as IV nicardipine drip, IV esmolol drip, IV labetalol, or IV hydralazine

(6) Additional adjunctive medications

- Adjunctive medications orderable via Opioid Withdrawal order set
 - Clonidine PO in particular may be helpful for managing autonomic symptoms. If unable to tolerate PO, consider utilizing the patch formulation.
- Can consider the use of phenobarbital (utilizing pre-existing ICU guidelines for managing alcohol withdrawal) or benzodiazepines (scheduled taper preferred over CIWA symptom-triggered dosing) if requiring additional sedation. Not routinely indicated, unless the patient also reports benzodiazepine or alcohol use.

Monitoring

- QTc once prior to first dose of methadone or olanzapine, and repeat prior to increasing methadone dose.
 - If QTc is > 500ms and HR is > 80 BPM, use the Hodges QTc correction formula to correct for heart rate
(<https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/calculators/corrected-qt-interval-qt-c-calculator/itt-20487211>).
 - Explanation: The MUSE automated reporting system uses the Bazett formula to calculate the QTc. The QTc will be more prolonged in sinus tachycardia than what is likely true repolarization due to the exponential term in the Bazett formula. The Hodges formula does not have an exponential term and provides a more accurate assessment of QTc at the extremes of HR.⁶
- COWs q4h
- Consider surveillance for myocardial ischemia or changes in myocardial function. Case reports have included myocardial injury.

⁶ PMID: 26552754

- Complete the following at baseline and every 4 hours for 24 hours after initiation or dose change:
 - Blood pressure, heart rate, respiratory rate, pulse oximetry
 - Pain score
 - Sedation score- POSS or RASS score per unit policy

- Contact covering provider for any of the following:
 - Respiratory rate less than 10 respirations/minute
 - SBP < 90 mmHg or MAP < 60 mmHg
 - POSS score of 3 or 4 (See below)
 - RASS score of +4, +3, +2, -3, -4 or -5 (See below)

Appendix: Sedation Scales

Pasero Opioid-Induced Sedation Scale (POSS)

S	Sleep, easy to arouse	Acceptable; no action necessary
1	Awake and alert	Acceptable; no action necessary
2	Slightly drowsy, easily aroused	Acceptable; no action necessary
3	Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3
4	Somnolent, minimal or no response to verbal or physical stimulation	Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory

The Richmond Agitation and Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive; vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (\geq 10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation

	-5	Unarousable	No response to voice or physical stimulation	
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