

Best Practices for Management of Xylazine Withdrawal and Xylazine-related Overdose

Xylazine is an alpha-2 agonist utilized as a veterinary sedative and increasingly prevalent in the illicit drug supply. It is thought to be an intentional adulterant added to illicit opioids for synergistic effects and/or to prolong the duration of short acting opioids (primarily fentanyl).

Xylazine and Opioid Withdrawal

Some patients with chronic fentanyl use who are co-exposed to xylazine may develop physiologic dependence and a withdrawal syndrome. There is little known about the characteristics, incidence, or severity of xylazine withdrawal syndrome. Patients and providers report/observe irritability, anxiety, restlessness and dysphoria. The possibility of additional autonomic effects, including tachycardia, diaphoresis and hypertension may occur in patients following xylazine abstinence within 8-24 hours. It is important to exclude (by detailed and collateral history, chart review, past and current drug screen results review when available) co-use of other agents (benzodiazepines or alcohol) and/or initiate prophylaxis or treatment of withdrawal syndromes associated with benzodiazepine or ethanol use when these autonomic symptoms are present.

Timing and monitoring

Opioid withdrawal may precede the onset of xylazine withdrawal or they may occur simultaneously. Early symptoms of anxiety, irritability and restlessness overlap with both opioid and xylazine abstinence syndromes. Initial symptoms may begin 6-12 hours following last use. Xylazine withdrawal may conflate the use of COWS scoring to determine buprenorphine readiness. The time course for opioid withdrawal onset has been skewed from historical descriptions of heroin withdrawal occurring within 6-12 hours of last use to onset of fentanyl withdrawal (depending on use pattern) which may be delayed to 12-24 hours prior to a measurable COWS score >8 or 12. In people with heavy fentanyl use, xylazine withdrawal may occur first and be interpreted as part of the opioid withdrawal syndrome. A hallmark of xylazine withdrawal is that additional doses of full agonist opioids do not improve symptoms. Supporting the patient to give input on whether their symptoms are from xylazine vs opioid withdrawal is often helpful.

Severe symptoms

In patients who progress to consistently elevated blood pressures, tachycardia (+/- tremulousness), adjunct therapies for symptom management may be necessary. Unlike benzodiazepine or alcohol withdrawal syndromes, progression to delirium has not been documented. Exceptionally rare cases of escalating blood pressure and agitation may warrant ICU level care and dexmedetomidine infusion may be needed.

What follows is an outline of strategies for prophylaxis and treatment of opioid withdrawal complicated by possible xylazine withdrawal. Caveats in the management of suspected xylazine overdose are included as

well.

The following strategies have been utilized to manage xylazine withdrawal. As this is a rapidly evolving challenge, this is a compendium of best practices derived from:

- 1) experiences in our health system
- 2) literature review
- 3) personal communication with expert colleagues

For ALL Patients: Expert guidance is available via consultation with addiction medicine, psychiatry - MEND or consult liaison services, or opioid stewardship pharmacist (HUP).

Prophylaxis and treatment of xylazine withdrawal –

First-line, for use in all patients unless contra-indicated

Clonidine: alpha2-adrenergic agonist; antihypertensive; efficacy in opioid withdrawal attributed to binding to central alpha-2 adrenergic receptor that shares potassium channels with opioids and blunts symptoms of withdrawal

- 0.1mg PO q6-8h scheduled (not PRN) and titrated to effect, up to a maximum dose of 0.3 mg PO Q8h
- Monitor for signs of hypotension and oversedation especially in patients with ESRD, advanced age or compromised renal function.

Pain and opioid withdrawal management

Concomitant initiation of medications for opioid use disorder (MOUD) with buprenorphine, methadone and/or short acting opioid agonists will optimize the opportunity to initiate OUD treatment. In addition, these medications will further support management of acute pain. See pathway (link to bup/methadone initiation pathway and to Short acting agonist pathway).

Gabapentin or pregabalin should be considered if comorbid pain and as adjunct to clonidine, MOUD and full opioid agonists unless contra-indicated. For gabapentin and pregabalin, use caution and lower starting doses in patients with AKI/CKD and older adults. See dosing information on the formulary. Ketamine should also be considered where available unless contra-indicated.

Gabapentin: anticonvulsant; 300-600 mg PO q8h and 300mg QHS;

Pregabalin: anticonvulsant; consider as alternative to gabapentin; 50-100mg PO TID

Ketamine: NMDA receptor antagonist; effective as opioid sparing analgesic adjunct; oral use

available in non ICU settings at HUP only; IV use restricted to critical care settings. Refer to respective formulary guidelines for clinical guidance and dosing. *Consider using for all patients where available, unless CI.*

Adjuncts for restlessness and/or agitation

Consider addition of any of the below agents if scheduled clonidine, gabapentin and ketamine (where available), in addition to full agonist and MOUD, are not sufficient to control symptoms.

Olanzapine: atypical antipsychotic. *Consider when compelling indications of N/V, insomnia, severe agitation or anxiety.*

- Consider starting dose of 5-mg x 1, then once-twice daily. Recommend lower doses (2.5 mg) for older adults or medically frail.

Hydroxyzine: *antihistamine; consider when compelling indications of severe anxiety*

- Recommended dosing 50 mg PO q6h (scheduled)

GABA agonists: *for use in comorbid alcohol or benzodiazepine withdrawal, for severe acute agitation or agitation.*

- Lorazepam 1-2 mg PO/IV/IM; titrate to effect OR
- Phenobarbital 65-130 mg PO/IV x 1; titrate to effect and as tolerated
 - Restricted to ICU and ED at PAH; check local hospital restrictions
- Monitor for sedation, respiratory depression and/or signs of delirium
- *Lorazepam and phenobarbital not intended to be used together*

Dexmedetomidine (ICU only): alpha 2 agonist; sedation; antihypertensive; *use in ICU settings after maximizing oral alpha 2 agonists: See formulary for dosing guidance.*

Link to dexmedetomidine formulary guidance

Clinical Effects and Overdose Management:

After xylazine administration, the onset of sedation is rapid (1-2min) and compounds the sedative effects of fentanyl. Naloxone should still be considered the primary effective antidote, since reversing the fentanyl co-intoxication will likely result in adequate respirations. Supportive care, including airway management, may be needed for patients with significant sedation and respiratory depression secondary to overdose; intravenous naloxone should be considered if intranasal naloxone has not restored sufficient

respiratory effort. Bradycardia and hypotension have been reported in intentional xylazine only overdoses, and these effects can occur from opioids. Sinus bradycardia is most often asymptomatic. Mild hypotension is

responsive to fluid administration.

References

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