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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

MEDETOMIDINE

THE NEXT BIG WAVE IN THE TURBULENT SEA OF DRUG ADULTERANTS

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project ECHO

SPEAKER DISCLOSURES

✓ Any conflicts of interest?

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Understand characteristics of medetomidine
2. Describe its significance as an emerging public heath concern
3. Identify & manage intoxication & withdrawal

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YOUR PATIENT, JENNIFER, WHO STRUGGLES WITH OUD, EXPERIENCES A PRESUMED FENTANYL-RELATED OVERDOSE OUTSIDE OF YOUR CLINIC …

- You're notified, rush out and find her profoundly sedated, with slow shallow breathing (though preserved perfusion/no cyansosis) and bradycardia (HR = 41 bpm).

- Naloxone X2 is given w/normalization of respiratory rate. However, sedation and bradycardia persist.

- EMS arrives, transports her to the ED

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EMS TRANSPORTS JENNIFER TO THE ED, WHERE…

- In the ED, she remains fairly sedated. EKG shows sinus bradycardia (HR now at 48), RR = 12, BP = 100/70, T= 97.
- Urine toxicology is positive for fentanyl and cannabis. BMP & CBC WNL. CT head non-concerning.

- 4hrs later…
  - Her sedation has cleared, but she did not return to her normal baseline. Instead, she transitions rapidly to extreme autonomic hyperactivity, with HR = 155 bpm and BP = 210/115 mmHg, accompanied by intractable vomiting, tremors, and agitated delirium.
  - Her team noted that symptom onset was unusually rapid and her BPs unexpectedly high for opioid withdrawal, though begin methadone empirically w/plan to admit....

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BACKGROUND

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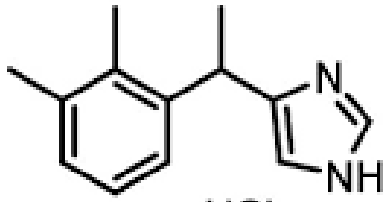
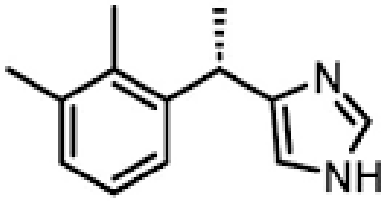
“MEDE” – WHAT!?



Medetomidine, 1



Dexmedetomidine, 2

- A sedative-anesthetic.
- A racemic mixture
  - –Racemic mixture is approved for veterinary use (most commonly in canines)
  - –d-enantiomer (dexmedetomidine, “Precedex”) produces nearly all pharmacological activity
  - –Dexmedetomidine (d-enantiomer) is FDA-approved for use in humans, used for partial sedation & anesthesia

https://www.sciencedirect.com/science/article/abs/pii/0278584689900511?via%3Dihub

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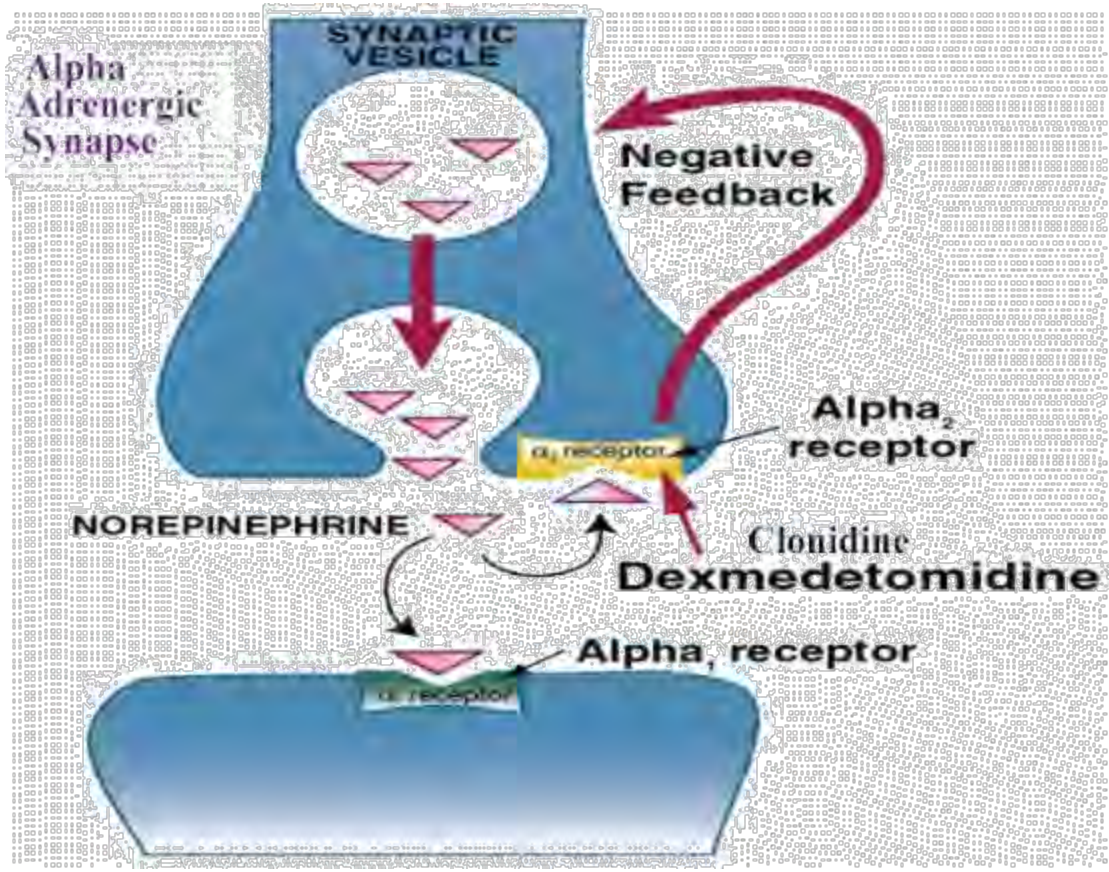
"MEDE" – WHAT!?

- Highly potent, selective α-2 adrenergic receptor agonist
  - α-2a/α-1 selectivity ratio: 1620 (vs. clonidine: 220; xylazine: 160)
  - Centrally: α-2a in brainstem & locus coeruleus → inhibits norepinephrine release
    - I.e., ↓ central sympathetic outflow
    - Unlike benzodiazepines/propofol: ↓ neuronal activity but preserves reactivity; partial sedation, not fully amnestic
  - Peripherally: (with higher doses or rapid admin) α-2b-adrenoceptors: vasoconstriction → HTN



https://transpopmed.org/articles/tppm/tppm-2018-5-070.php

https://www.sciencedirect.com/science/article/abs/pii/0014299988907443?via%3Dihub
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010269.pub2/full
https://pubmed.ncbi.nlm.nih.gov/28626012/
https://pubmed.ncbi.nlm.nih.gov/23761387/
https://pubmed.ncbi.nlm.nih.gov/41101830/

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PHARMACOKINETICS* (BASED ON DEXMEDETOMIDINE, IV)

- High lipophilic → rapid CNS penetration
  - –Rapid onset of action (~5-10min) & time to peak effect (15-30min)
  - –Major metabolic pathway: hepatically metabolized (N-glucuronidation), urinary excretion
- Half-life (terminal): approximately 1.3-3 hours (2 to 4 hours in ICU patients)
  - –Prolonged, in setting of hepatic impairment

* Based primarily on data from IV dexmedetomidine, with inference from observational studies of non-rx'd racemic mixtures.

https://www.uptodate.com/contents/dexmedetomidine-drug-information?source=auto_suggest&selectedTitle=1~1---1~4---dexmed&search=dexmedetomidine

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EFFECTS (DOSE-DEPENDENT)

Major Effects

- **Sedation/decreased vigilance**
- **Anxiolysis**
- **Analgesia**
- **Bradycardia** (down to 30-40s)
- **Hypotension** (often mild)
- **Limited bradypnea, except at high doses**

Minor effects

- Hypothermia & Anti-shivering
- Mydriasis
- Dieresis
- Reduced GI motility & gastric acid
- Anti-delirium (+/-)

https://pubmed.ncbi.nlm.nih.gov/23761387/
https://pubmed.ncbi.nlm.nih.gov/41101830/
https://pubmed.ncbi.nlm.nih.gov/40396666/

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EPIDEMIOLOGY TRENDS & DRIVERS

- ↑ in the US since 2022
  - Prevalence varies by region
  - Referred to as “rhino tranq”, “mede”, or “dex”, others
- Rapid ↑in drug supply
  - Forensic Lab reports: 245 (2023) → 2,276 (2024)
  - In Fentanyl samples:
    - Up to 63.6% nationally, 89.1% in Northeast
  - Has also been found in stimulants/other opioids
  - Often replacing Xylazine (though these co-occur in many samples)
    - Note: not associated with xylazine’s necrotic wounds
  - Cheap (powder from India/China; potentially synthesized by cartels)

https://pubmed.ncbi.nlm.nih.gov/40889436/
https://pubmed.ncbi.nlm.nih.gov/40338638/

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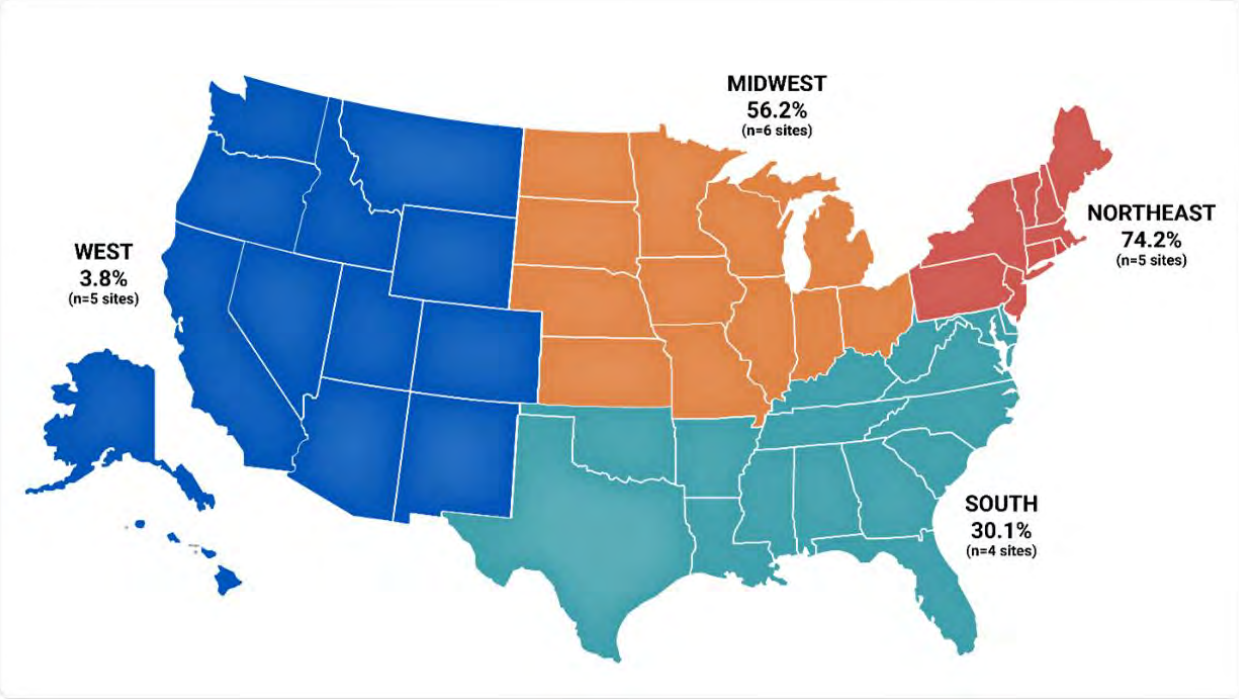
WHY THIS MATTERS – RISING PREVALENCE

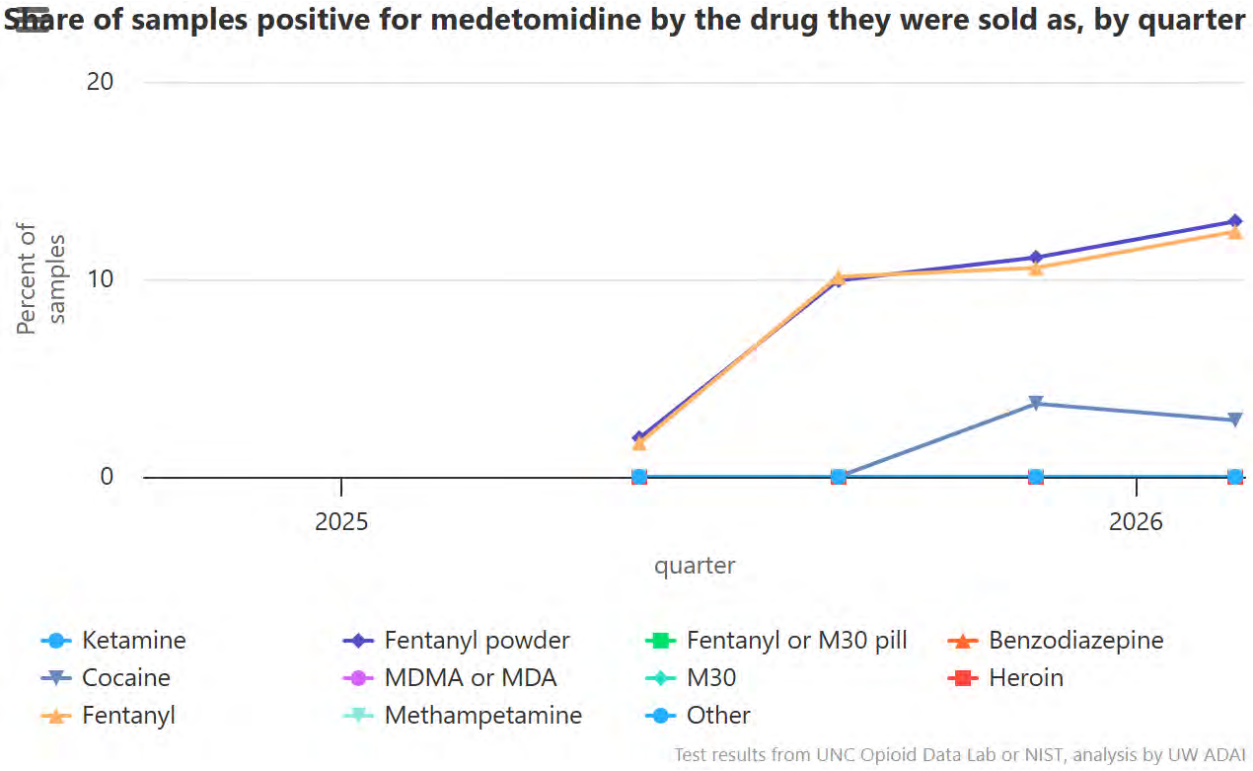
Nationally

Figure: Percentage of opioid-positive drug product and paraphernalia samples also positive for medetomidine across 20 sentinel sites[a]: US region, July 2025–December 2025 (Provisional data)[b,c]



https://www.cdc.gov/han/php/notices/han00527.html

Washington State



https://adai.uw.edu/WAdata/DrugChecking/medetomidine.html

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WHY THIS MATTERS – CLINICAL SIGNIFICANCE

- Adds another layer of OD risk
- Potential for severe withdrawal
  - –Can complicate OUD care

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INTOXICATION

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TOXIDROME COMPARISON

Opioids:

- Sedation
- Respiratory depression (rate consistently, tidal volume more variable)
- Miosis
- Decreased bowel sounds
- Responsive to mu-receptor antagonists (naloxone)

α-2 Agonists (Medetomidine)

- ***Bradycardia*** (perhaps most salient finding)
  - ~40bpm
- Sedation (< opioids ***but*** can be significant & prolonged)
- Mild respiratory depression (at high doses, but synergistic w/opioids)
- +/- hypotension, hypothermia
- +/-hallucinogenic effects (17.6% vs 1.2% in higher concentration vs trace-level samples)
- *No response to naloxone*

https://doi.org/10.1080/15563650.2025.2500601
https://pubmed.ncbi.nlm.nih.gov/40310760/
https://pubmed.ncbi.nlm.nih.gov/40843624/)
https://pubmed.ncbi.nlm.nih.gov/41575403/

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INTOXICATION: TIMELINE

Timelines for symptom remission vary with dosing, co-intoxication.

- **Bradycardia**: median ~3.4 hours (but can be prolonged)
- **Sedation:**
  - Appears to covary with duration of bradycardia,
  - Also impacted by copresence of other sedating substances (fentanyl, xylazine)
- **Post-acute observation periods:** typically ≥ 3 to 6 hours for resolution of acute intoxication

https://pubmed.ncbi.nlm.nih.gov/40396666/
https://pubmed.ncbi.nlm.nih.gov/41575403/

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ASSESSMENT ALGORITHM – INTOXICATION

- Obtain history (as able), conduct PE, toxicology (if possible)

- Dx challenges:
  - Tox Screens: many routine immunoassays don't include medetomidine
    - Specialty LC & MS: time-delayed & expensive
    - Medetomidine is rapidly metabolized
    - Therefore, for now diagnosis is clinical
  - Most patients unaware of exposure
  - Polysubstance exposure is the norm
    - Sign/symptom-overlap exists btwn opioids, sedatives, α-2 Agonists, other intoxicants

https://pubmed.ncbi.nlm.nih.gov/41575403/

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INITIAL MANAGEMENT ALGORITHM – INTOXICATION

1. Airway / Respiratory Support (PRN)
2. Naloxone
3. Monitor (VS, MS, Tele) + Supportive Care (fluids/O2)
4. Rx (rare): atropine, pressors
5. Intubation PRN (rarely)

https://pubmed.ncbi.nlm.nih.gov/40396666/
https://pubmed.ncbi.nlm.nih.gov/40310760/

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INTOXICATION – DISPOSITION

[No truly evidence-based criteria, but can consider the following]

Consider Admission for:

- Persistent bradycardia (~ > 4-6 hours)
- Hemodynamically significant bradycardia
- Profound sedation preventing safe discharge
- Significant other medical complications/comorbidities impacting safety

Safe Discharge Criteria Might Include:

- Resolution of Bradycardia & other VSS
- Return to baseline mental status
- Following observation period: ≥ 6-8 hours (?) w/o emergence of withdrawal
- Appropriate other SUD treatment plan, provision of naloxone kit, etc.

https://pubmed.ncbi.nlm.nih.gov/41575403/
https://pubmed.ncbi.nlm.nih.gov/40396666/

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INTOXICATION: OUTCOMES

Treatments and Outcomes (Case Series (N=11)):

- **All patients survived**
  - 55% admitted to hospital
  - Only 1 patient required ICU care
- **No patients required**:
  - Atropine for bradycardia
  - Electrical pacing
  - Vasopressors
- **Key message**: Most managed with supportive care only

https://pubmed.ncbi.nlm.nih.gov/40396666/

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WITHDRAWAL

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WITHDRAWAL(S) – OPIOID + MEDETOMIDINE

- **Opioid withdrawal** progression is **(fairly) predictable & very treatable**
  - –Prolonged ED stay or observation periods are rare
  - –Medetomidine further complicates prognosis & safe disposition
- **Medetomidine withdrawal:**
  - –Variable progression + limited experience = uncertainty.
  - –Usually begins earlier than other syndromes (~often w/in 4-6 hrs of last use)
    - However, some pts may have milder symptoms that gradually progress over 24hrs
  - –Previous severe withdrawal: likely best predictor of future severe withdrawal.

https://pubmed.ncbi.nlm.nih.gov/41575403/

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WITHDRAWAL OVERVIEW

A distinct syndrome

- Relative to Opioids
  - Some symptomatic overlap, but also are distinctive features (see below)
  - Differing timeline (earlier onset)
  - Not responsive to opioid rx)
- Relative to xylazine: significant HTN & tachycardia

Characterized by **sympathetic surge / catecholamine rebound**

- Hypertension (often significant, BP >200/100s)
  - Complications such as PRES and NSTEMI have been (rarely) observed
- Tachycardia
- Agitation/Delirium
- Vomiting
- Other: diaphoresis, tremor, anxiety
- [If these are not responsive to MOUD, consider medetomidine withdrawal]

https://penncamp.org/medetomidine/

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Outpatient Medetomidine Withdrawal Treatment Guideline

Recognize Withdrawal

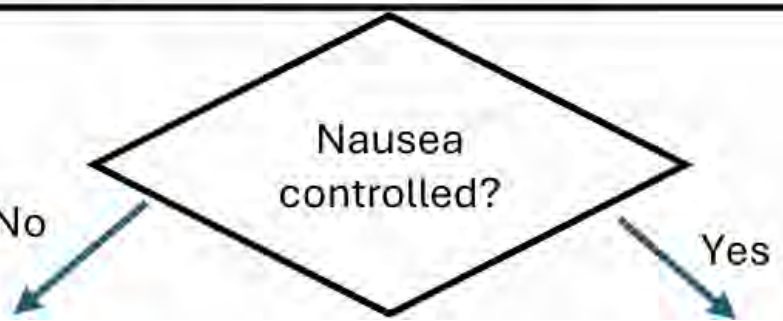
Medetomidine clinical withdrawal symptoms may include:

- Onset within hours of last illicit substance use
- Nausea and vomiting
- Tremor, myoclonic jerks
- Anxiety
- Diaphoresis
- Sinus tachycardia, potentially significant (>120 bpm)
- Hypertension, potentially severe (SBP>170mmHg, DBP>100mmHg)
- Encephalopathy/delirium in severe cases
- Minimal response to symptomatic therapies

Treat Nausea (early & aggressive)

Early aggressive anti-emetic therapy:

- Ondansetron rarely effective, prefer dopamine antagonist
- 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

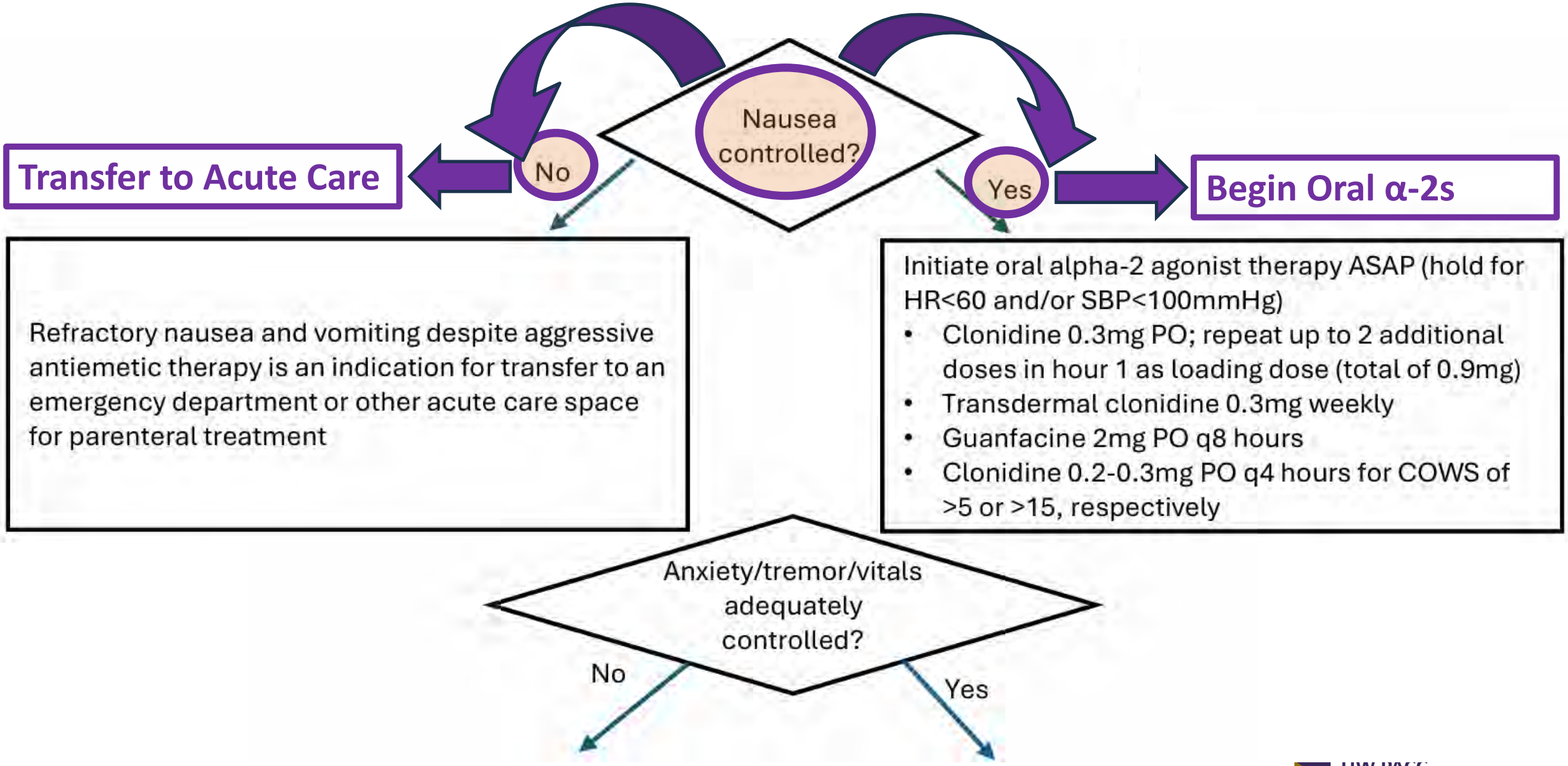


Other findings and considerations:

- Elevated lactic acid with acidosis
- Hypokalemia
- Myocardial injury and cardiomyopathy
- PRES due to hypertension
- QTc prolongation
- Severe withdrawal uncontrolled with oral medications requires hospital (ED/ICU) care

Medetomidine Outpatient Withdrawal Guidelines

OUTPATIENT MEDETOMIDINE WITHDRAWAL MANAGEMENT



[Medetomidine Outpatient Withdrawal Guidelines]

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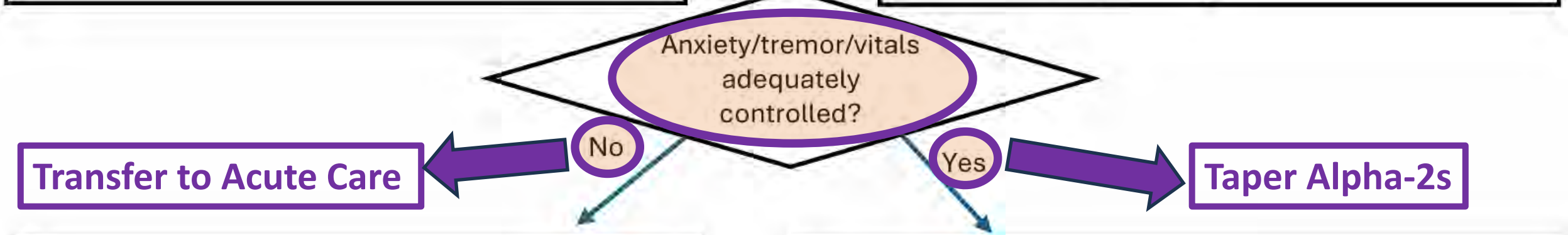


Poorly or uncontrolled symptoms and/or dangerous elevations in heart rate and blood pressure despite aggressive oral alpha-2 agonist therapy are indications for transfer to an emergency department or other acute care space for parenteral treatment

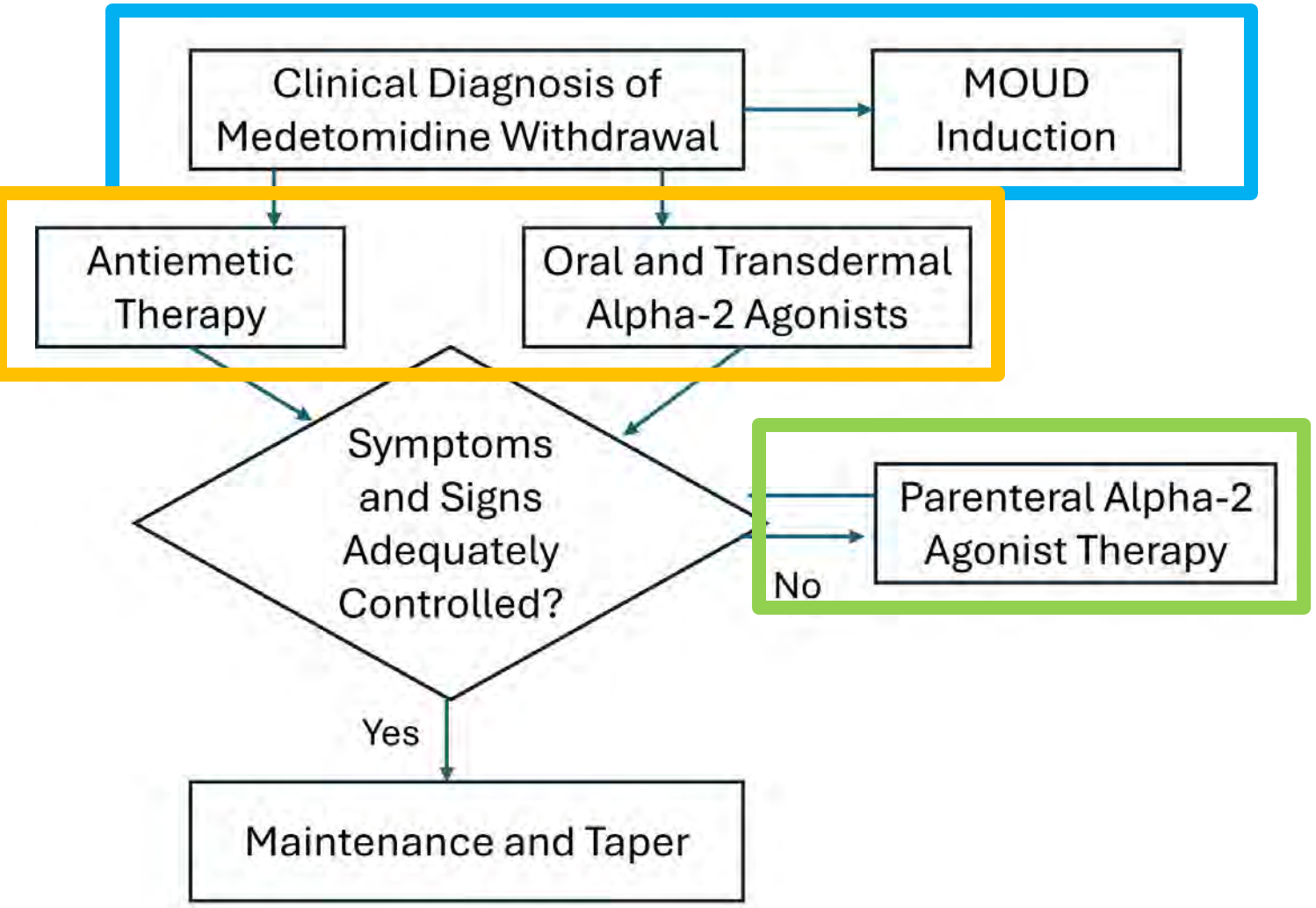
Wean as tolerated:

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

Concurrent opioid withdrawal and opioid use disorder care:

- Medetomidine withdrawal symptoms overlap but precede severe opioid withdrawal, so patients remain at risk for precipitated withdrawal despite significantly elevated COWS scores
  - Proceed with typical buprenorphine induction processes that mitigate risk of precipitated withdrawal after initiating symptomatic treatment and alpha-2 agonists
- Methadone initiation can occur simultaneously with alpha-2 agonist treatment
  - Monitor QTc as some patients exhibit this when experiencing medetomidine withdrawal

ED/INPATIENT WITHDRAWAL ALGORITHM



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 1mg PO TID x 1 day, then 1mg PO BID x 1 day, and 1mg PO once x 1 day and remove clonidine patch
- Other symptom-triggered medications as needed

https://doi.org/10.1016/j.annemergmed.2025.12.004

OUTCOMES:

From a pragmatic retrospective cohort analysis (chart review, n=101) in Acute Care Setting

Table 5. Withdrawal clinical outcome summary. A tally of clinical treatment and outcomes for those suffering from withdrawal symptoms from the cohort. This includes patients with primary intoxication phenotype who later developed withdrawal symptoms.

Outcome	All Patients (n = 100)
Dexmedetomidine Infusion	63 (63%)
Clonidine PO use	89 (89%)
Clonidine Transdermal Patch use	78 (78%)
NSTEMI/hsTnT Elevation > 53 ng/L	20 (20%)
Encephalopathy as diagnosis or PRES	31 (31%)
Seizure During Visit	5 (5%)
Highest COWS Score	23 (19–28)

https://pmc.ncbi.nlm.nih.gov/articles/PMC12295796/

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JENNIFER'S STORY, CONTINUED…

- Recall…She presented to ED with HR = 155 bpm & BP = 210/110, intractable vomiting, tremors, and agitated delirium. COWS = 25. Admitted to medicine.
- A team member – who'd just relocated to WA from NY – reviewed the chart, examined the pt, and hypothesized that she may be experiencing medetomidine withdrawal.
- Initial Rxs:
  - Methadone 40mg + 10mg + 10mg over 2hr were given (w/no appreciable effect)
  - IV Olanzapine 5mg X 2 for nausea
  - Clonidine:
    - PO: 0.3mg X 2 in 1hr, then 0.2-0.3mg PO q4h hours for COWS of >5 or >15, respectively
- Reassessment at 3hrs showed persistent tachycardia (HR = 140s) & HTN (200/112), COWS = 23, encephalopathy persists.
  - Dexmedetomidine started
    - Bolus: 1mcg/kg x 1
    - Infusion: started at 0.5mcg/kg/hr and titrated to 1mcg/kg/hr

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JENNIFER'S STORY, CONTINUED…

Next 24hrs:

- Autonomic instability, agitation, nausea improved with dexmedetomidine infusion.
- Methadone continued, titrated (pt preferred over buprenorphine)
- Clonidine:
  - Patch: 0.3mg/24hr (7day) placed
  - PO: 0.2-0.3mg PO q4h hours for COWS of >5 & 15, respectively

Subsequent 24hrs:

- Dexmedetomidine successfully tapered after 28hr, w/overlapping clonidine.
- Guanfacine 2mg TID initiated
- Clonidine patch and PO PRNs continued (though w/decreasing dose & frequency)
- Methadone titrated based per usual protocol

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JENNIFER'S STORY, … CONCLUDED.

HD# 3: Discharged with

- Guanfacine 1mg TID X 1 day, then tapered by 1mg/day
- Clonidine:
  - Patch: 0.3mg/24hr (discontinued with guanfacine)
  - PO: 0.1-2mg PO q4h hours for subjective withdrawal (hold for dizziness)
- Methadone: titrated to 90mg Qday
- Naloxone

- Follow-up arranged:
  - Methadone Clinic intake scheduled for day after discharge
  - Urgent PCP follow-up appointment scheduled

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OTHER CONSIDERATIONS

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OUTPATIENT CONSIDERATIONS

Talk to your patients: assess knowledge, query experience, provide education

- Increased overdose risk with polysubstance mixtures
- 200–300x stronger than xylazine
- Prolonged sedation & bradycardia (+/- unexpected PD) suggestive
- Drug checking (POC drug test strips increasingly available)
- Naloxone = essential! (Opioids nearly always co-present)
- Never use alone

Clinical Care:

- Identify atypical intoxication & withdrawal patterns
- Use antiemetics & α-2 agonists (e.g., clonidine, guanfacine)
- Don't forget MOUD, naloxone!
- Provide close follow-up

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PUBLIC HEALTH CONSIDERATIONS

- Community-level response required
  - –Clusters can emerge rapidly
  - –Multisector surveillance essential: Healthcare providers, labs, public health
- Notify local/county Public Health Dept (or WA DOH PH Lab (206-418-5500)) when medetomidine suspected/confirmed

https://pubmed.ncbi.nlm.nih.gov/40257270/
https://www.cdc.gov/mmwr/volumes/74/wr/mm7415a1.htm

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KEY TAKEAWAYS

- Medetomidine is a potent, **selective α-2a agonist** used in **veterinary medicine as a sedative-analgesic**
- ↑ **prevalent fentanyl adulterant**, often co-detected with (but replacing) xylazine
  - Can complicate opioid intoxication/OD & withdrawal management

- Clinical Presentation:
  - Intoxication: bradycardia (<50 beats/min), sedation not fully responsive to naloxone
  - Withdrawal: early onset/rapid progression, with significant tachycardia, hypertension, N/E, delirium

- Clinical Management:
  - Intoxication/OD: supportive care & monitoring (naloxone for opioid overdose)
  - Withdrawal: early α-2 agonists like clonidine or (inpt) dexmedetomidine.
  - For assistance, can call Washington Poison Center at (800) 222-1222, local Addiction Consult Service

- Notify local/county Public Health Dept (or WA DOH PH Lab (206-418-5500)) for confirmed or suspected cases (esp clusters)

- Other resources:
  - https://vimeo.com/1078755974?share=copy#t=0
  - https://www.cdc.gov/han/php/notices/han00527.html

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THANKS

&

DISCUSSION

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