Tranq Dope: Practical Lessons from the Epicenter of the Xylazine Crisis

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Disclosure Information

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  - No Disclosures
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  - No Disclosures
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  - No disclosures
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  - No disclosures

Learning Objectives

Become familiar with Xylazine trends and epidemiology

Describe Xylazine pharmacology and pharmacokinetics

Describe withdrawal and pain management methods

Identify additional considerations: Wounds, harm reduction, and pregnancy/lactation

Case

- MJ is a 32 yo woman with known OUD (active IV use), anxiety, and hypertension brought in by EMS to the ED after being found down on the street. She received two doses of intranasal naloxone in the field which restored breathing.
- In the ED, MJ continues to be somnolent
  - BP 98/62 mmHG | HR 55| RR 6

What should we do?

A. Give 4mg IN naloxone
B. Give 0.04mg IV naloxone
C. Give 0.4mg IV naloxone
D. Watch and wait

Poll: How often are you seeing Xylazine use in your patients?

Xylazine Trends in Philadelphia

- 344 samples analyzed between January – June 2023
- 99% of dope samples contained fentanyl and its analogues
- 98% of dope samples contained xylazine
- 16% of coke, 6% of crack, and 9% of meth contained xylazine
- Average amount of fentanyl in dope samples remained mostly consistent while the average amount of xylazine increased 34%

Table 2: Average Drug Content in Dope Samples

Quarter / Year ▸	Q3 2022	Q4 2022	Q1 2023	Q2 2023
Fentanyl (%)	12.4%	13.1%	14.9%	13.9%
Xylazine (%)	34.3%	38.5%	39.5%	46.1%

cfsre NPS DISCOVERY Department of Public Health CITY OF PHILADELPHIA

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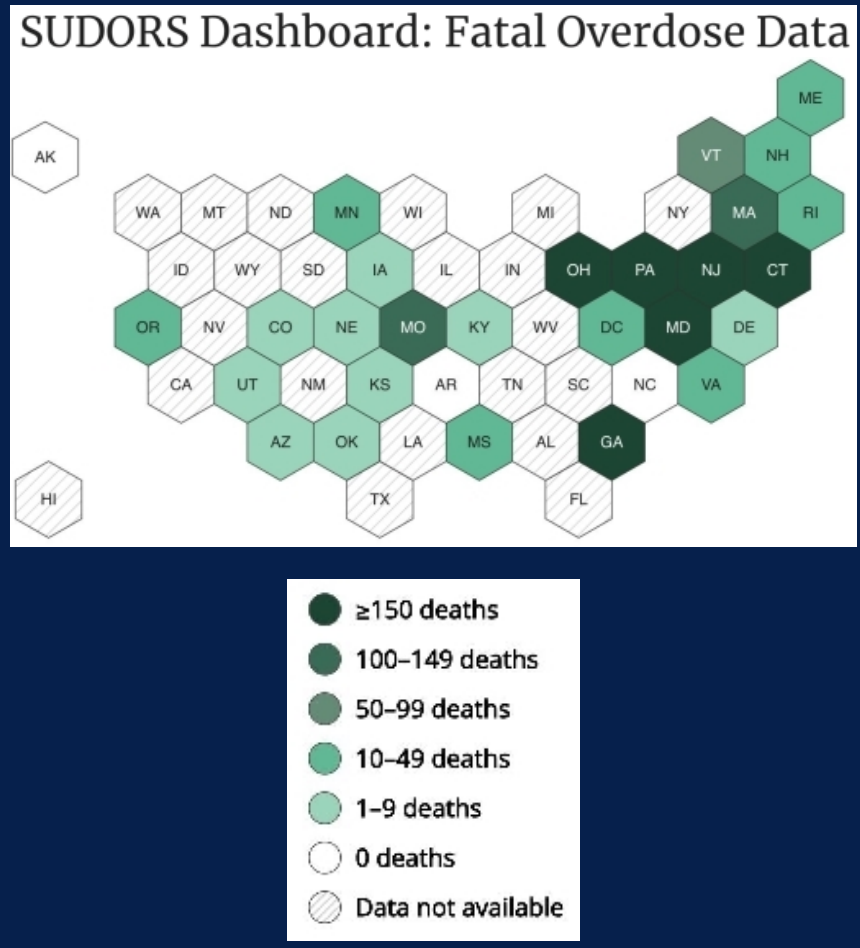
National Trends in Xylazine Prevalence

- Cano et al 2024:
  - 16 states with no xylazine forensic reports in 2019
  - Only 2 states WITHOUT xylazine forensic reports in 2022
  - At least 43 states reported at least 1 xylazine-related overdose death from 2019-2022
- Friedman et al 2022:
  - Among 10 jurisdictions (representing all four US Census Regions), prevalence rose from 0.36% of overdose deaths in 2015 to 6.7% in 2020
- SUDORS (CDC's State Unintentional Drug Overdose Reporting System):
  - Among 20 states and D.C., the monthly percentage of deaths involving fentanyl with xylazine increased from 3% in January 2019 to 11% in June 2022



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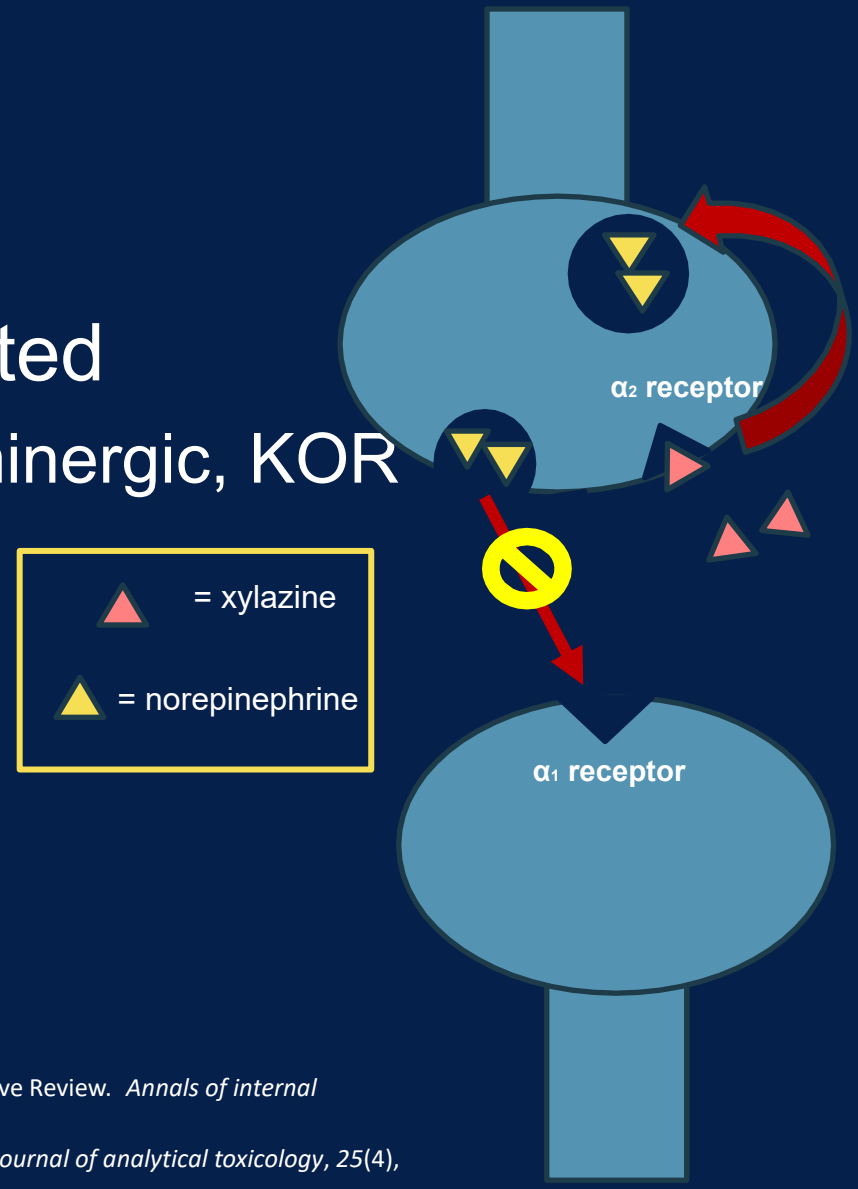
Pharmacology and Pharmacokinetics of Xylazine

Mechanism of Action

- α-2 adrenergic agonist
  - Decreased sympathetic outflow = sedation
- Additional action at other receptors suspected
  - Cholinergic, serotonergic, dopaminergic, histaminergic, KOR
- Similar to imidazolines
  - clonidine, dexmedetomidine, etc.



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Hoffmann, U., Meister, C. M., Golle, K., & Zschiesche, M. (2001). Severe intoxication with the veterinary tranquilizer xylazine in humans. *Journal of analytical toxicology*, *25*(4), 245–249. https://doi.org/10.1093/jat/25.4.245

Time to Effect & Duration

- Rapidly absorbed
  - Time to effect is 1-2 minutes with IV use
  - May be extended to 15 minutes with other routes (IM, SC, PO, IN)
- Highly lipophilic
  - Duration of effect is up to 4 hours (2-4+)
- Rapidly eliminated, processed in liver, excreted by kidneys
  - CYP450 interactions
  - Likely lasts in urine for 24-48 hours

D'Orazio, J., Nelson, L., Perrone, J., Wightman, R., & Haroz, R. (2023). Xylazine Adulteration of the Heroin-Fentanyl Drug Supply : A Narrative Review. *Annals of internal medicine, 176*(10), 1370–1376. https://doi.org/10.7326/M23-2001

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Xylazine Intoxication

- Spadaro et al 2023: survey of 61 people via Reddit
  - 81% increased overdose/passing out
  - 74% do not intentionally seek out xylazine
  - Intranasal (57%) and injection (43%) use most common
- Reed et al 2022: qualitative study of PWUD in Philadelphia

"It's called xylazine… philly's got that "tranq dope".. puts you out but you get addicted to that along with the fent!"

"…it's a waste of money because it don't hold you for jack. Don't have legs whatsoever. Don't have no kinda legs."

"They'll pass out somewhere, get robbed, won't remember what happened. All kinda crazy stuff."

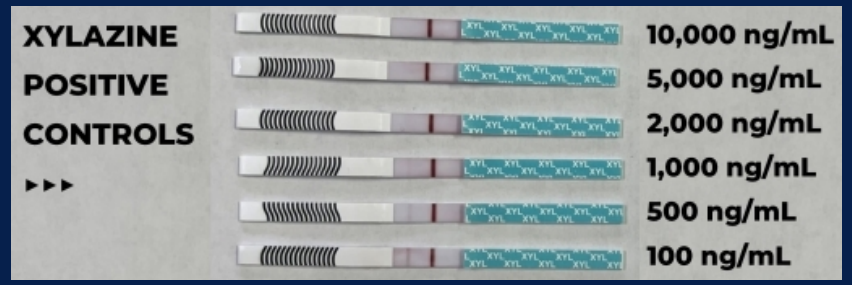
"I have basically blackouts from the tranq. I lose days at a time."

Spadaro A, Connor KO, Lakamana S, Sarker A, Wightman R, Love JS, Perrone J. Self-reported Xylazine Experiences: A Mixed Methods Study of Reddit Subscribers. medRxiv [Preprint]. 2023 Mar 14:2023.03.13.23287215. doi: 10.1101/2023.03.13.23287215. PMID: 36993695; PMCID: PMC10055471.

Reed, M. K., Imperato, N. S., Bowles, J. M., Salcedo, V. J., Guth, A., & Rising, K. L. (2022). Perspectives of people in Philadelphia who use fentanyl/heroin adulterated with the animal tranquilizer xylazine; Making a case for xylazine test strips. *Drug and alcohol dependence reports*, *4*, 100074. https://doi.org/10.1016/j.dadr.2022.100074

Role of Toxicology Testing

- Plasma testing is not widely available
  - No point of care testing commercially available
  - Urine testing is available at Penn
- Serum levels can be obtained through advanced testing
  - Mass spectrometry / thin layer chromatography



- One case report of severe xylazine intoxication with suicidal intention revealed 4.6 mg/L in plasma, 446 mg/L in gastric fluid, 194 mg/L in urine
  - Not enough data to determine "therapeutic vs toxic" levels in humans
- Test Strips
  - False + with lidocaine, levamisole, diphenhydramine, MDMA, methamphetamine
  - CFSRE: 100% sensitive, 85% specific
  - Sisco: xylazine detected in samples where concentration > 2mcg/mL

Hoffmann, U., Meister, C. M., Golle, K., & Zschiesche, M. (2001). Severe intoxication with the veterinary tranquilizer xylazine in humans. *Journal of analytical toxicology*, *25*(4), 245–249. https://doi.org/10.1093/jat/25.4.245

Sisco, E., Nestadt, D. F., Bloom, M. B., Schneider, K. E., Elkasabany, R. A., Rouhani, S., & Sherman, S. G. (2023). Understanding sensitivity and cross-reactivity of xylazine lateral flow immunoassay test strips for drug checking applications. *Drug testing and analysis*, 10.1002/dta.3612. Advance online publication. https://doi.org/10.1002/dta.3612

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Management of Polysubstance Overdose

Xylazine Overdose

- Similar to that of other α-2 agonists:
  - CNS depression: drowsiness/fatigue (common), LOC/apnea requiring intubation (rare)
  - Bradycardia, hypotension (fairly mild)
  - Miosis
  - Hyperglycemia?
  - Transient anemia?

Ball, N. S., Knable, B. M., Relich, T. A., Smathers, A. N., Gionfriddo, M. R., Nemecek, B. D., Montepara, C. A., Guarascio, A. J., Covvey, J. R., & Zimmerman, D. E. (2022). Xylazine poisoning: a systematic review. *Clinical toxicology (Philadelphia, Pa.)*, *60*(8), 892–901. https://doi.org/10.1080/15563650.2022.2063135

Seger, D. L., & Loden, J. K. (2018). Naloxone reversal of clonidine toxicity: dose, dose, dose. *Clinical toxicology (Philadelphia, Pa.)*, *56*(10), 873–879. https://doi.org/10.1080/15563650.2018.1450986

In & Out of Hospital Treatment

- Naloxone largely ineffective
  - Typical doses used for opioids (up to 2 mg, in studies) ineffective
  - Needs study: larger doses similar to those used for other imidazoline overdose (eg, clonidine), 0.1 mg/kg up to 10 mg total
- Alpha-adrenergic antagonists = reversal agents
  - Atipamezole, tolazoline, yohimbine
  - Used in veterinary medicine for post-procedure sedation, not approved for use in humans
- Current recommendations:
  - Most overdoses are a combination of xylazine and opioid, so use naloxone!
  - High suspicion for xylazine overdose if unresponsive to naloxone
  - Supportive care

Seger, D. L., & Loden, J. K. (2018). Naloxone reversal of clonidine toxicity: dose, dose, dose. *Clinical toxicology (Philadelphia, Pa.)*, *56*(10), 873–879. https://doi.org/10.1080/15563650.2018.1450986

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Greenberg, M., Rama, A., & Zuba, J. R. (2018). Atipamezole as an emergency treatment for overdose from highly concentrated alpha-2 agonists used in zoo and wildlife anesthesia. *The American journal of emergency medicine*, *36*(1), 136–138. https://doi.org/10.1016/j.ajem.2017.06.054

Case Continued

- MJ remains in the ED after receiving 2 doses of intranasal naloxone and one dose of 0.04mg IV naloxone.
- MJ is having a hard time engaging in conversation as she continues to experience sedation.
  - BP: 105/92 | HR: 68 | RR: 10

What should we do?

A. Give 0.04mg IV naloxone

B. Give 0.4mg IV naloxone

C. Watch and wait

Medical Withdrawal Management

Xylazine Withdrawal

- Chart review of 73 patients at Penn with urine xylazine detected
  - High variability but anxiety and restlessness reported most frequently by patients
  - Majority *without* new withdrawal syndrome distinct from opioid withdrawal
- Survey of 61 people who have used xylazine identified via Reddit
  - 53% reported having withdrawal from xylazine
  - Symptoms include: anxiety (91%), depressed mood (74%), and body aches (63%)
  - Majority (57%) reported xylazine made withdrawing from other substances worse

"I'm on 80 mgs of methadone…I would get a few bags here or there. Thinking ahh I got the methadone to fall back on and I'll be fine.. well come to find out the shit is heavily cut with xylazine"

"…tranquilizer is the worst habit to kick because apparently it takes two to four weeks to get off of it."

"Suboxone and methadone don't help if there is tranq in your dope".

Spadaro A, Connor KO, Lakamana S, Sarker A, Wightman R, Love JS, Perrone J. Self-reported Xylazine Experiences: A Mixed Methods Study of Reddit Subscribers. medRxiv [Preprint]. 2023 Mar 14:2023.03.13.23287215. doi: 10.1101/2023.03.13.23287215. PMID: 36993695; PMCID: PMC10055471.

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Thakrar, Ashish et al. Xylazine Testing & Withdrawal Among Hospitalized Patients in Philadelphia, Penn CAMP Xylazine Best Practices, 2023. PennCamp.org

Poll: Which of the following are you utilizing for management of Xylazine withdrawal?

Withdrawal Management

- Based on expert-opinion, case studies, no RCTs
- Medications include
  - Alpha-agonists
  - Ketamine
  - Sedatives/antipsychotics (olanzapine)
- Used in addition to opioid withdrawal management with:
  - MOUD = saves lives
  - Symptoms from xylazine withdrawal may heighten patient fears of precipitated withdrawal
  - Opioid agonists as needed
- Special considerations in pregnant population

Ehrman-Dupre R, Kaigh C, Salzman M, Haroz R, Peterson LK, Schmidt R. Management of Xylazine Withdrawal in a Hospitalized Patient: A Case Report. J Addict Med. 2022 Sep-Oct 01;16(5):595-598. doi: 10.1097/ADM.0000000000000955. Epub 2022 Jan 11. PMID: 35020700.

Withdrawal Management: Alpha-Agonists

- α2-adrenergic receptor agonists
- Decrease activity of noradrenergic neurons

- Dexmedetomidine
  - Widely available in IV infusion or pushes, but often limited to ICU
  - Infusion: 0.2 to 1.5 mcg/kg/hour (uptitrate q30min)
  - SE: Bradycardia (heart block), hypotension, hypertension
- Clonidine
  - Oral: 0.1 to 0.3 mg every 6 to 8 hours
  - Hypotension (often limits dose), bradycardia
- Tizanidine
  - Oral: 2 to 8mg every 8 hours

- Caution in renal and hepatic failure
- May enhance effects of beta-blockers

Withdrawal Management: Ketamine

- N-methyl-D-aspartate (NMDA) receptor antagonist
  - Serotonin and dopamine reuptake inhibition, activity at kappa and norepinephrine receptors, and activity at calcium, sodium and potassium channels
- Dose-dependent effect
- Case studies describe use of ketamine to mitigate precipitated withdrawal

- Oral
  - undergoes first pass metabolism with active metabolite
  - Starting dose 10-20mg q6h
  - Peak 30m
  - Increase by 10mg per dose every 12-24h
  - Usual max 50mg q6h
  - Typical effective dose: 1.5-3mg/kg/day

- IV infusion
  - Bolus: 0.1-0.5mg/kg over 2-15 minutes
  - Starting infusion: 0.1-0.2mg/kg/hr (or higher)
  - Can increase q30-60 min
  - Usual effective dose 0.1-0.5mg/kg/hr

Gupta, A., Devi, L. A., & Gomes, I. (2011). Potentiation of μ-opioid receptor-mediated signaling by ketamine. *Journal of neurochemistry*, *119*(2), 294–302. https://doi.org/10.1111/j.1471-4159.2011.07361.x

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Christian, N. J., Butner, J. L., Evarts, M. S., & Weimer, M. B. (2023). Precipitated Opioid Withdrawal Treated With Ketamine in a Hospitalized Patient: A Case Report. *Journal of addiction medicine*, *17*(4), 488–490. https://doi.org/10.1097/ADM.0000000000001151

Withdrawal Management: Sedatives/Antipsychotics

Medication	MOA	Dose	Considerations
Benzodiazepines	Potentiate GABA-A receptors, enhancing release of inhibitory neurotransmitter	*Clonazepam 0.5mg q8h, Chlordiazepoxide 25mg TID, Diazepam 10mg q8h	Long-acting preferred; highly addictive, *often comorbid BUD
Gabapentin / pregabalin	Unclear; voltage-gated calcium channels; reduces release of excitatory neurotransmitters	Gabapentin 300-600mg q8h (increase by 300mg per dose q2-3 days) Pregabalin 75-150mg q12h	Reduce dose in renal impairment
Phenobarbital	Prolongs and potentiates GABA-A receptors	32.4-64.8 mg q6h PRN	Very long half-life; Reduce dose in renal/hepatic impairment
Olanzapine	$5HT_{2A}$, $5\text{-}HT_{2C}$, $D_{1\text{-}4}$, H_1, and $alpha_1$ antagonism	5mg q12h (can increase to 10mg q12h on Day 2)	

Lexicomp Online, Pharmacology: Mechanism of Action. Waltham, MA: UpToDate, Inc., 2024. https://online.lexi.com. Accessed February 2, 2024.

Case Continued

- MJ is transferred to the floor to undergo sepsis workup. Her mental status starts to improve and she reports severe pain due to leg wounds and withdrawal symptoms including restlessness, anxiety, and body aches. You suspect she may be experiencing opioid and xylazine withdrawal.

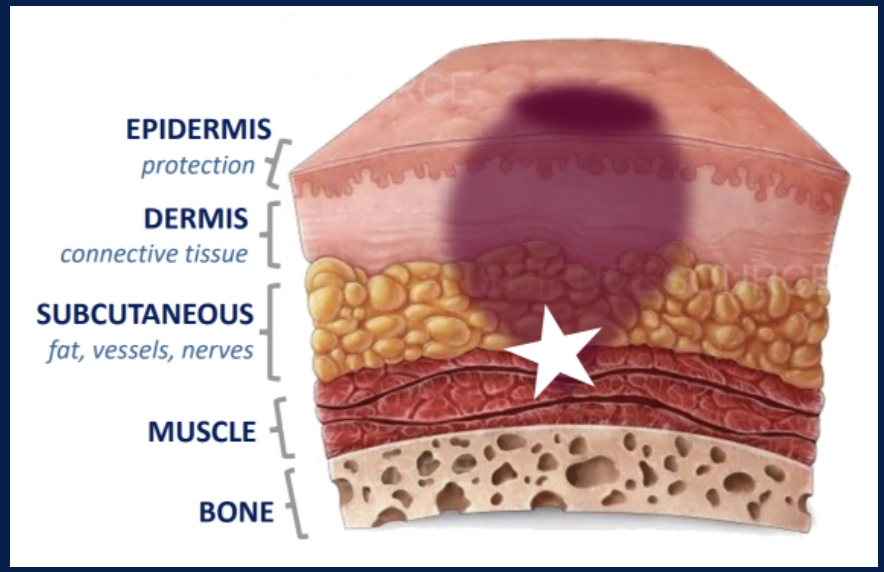
Which agent(s) should we use to treat MJ's withdrawal?

A. Ketamine 10mg PO q6h
B. Olanzapine 5mg PO q12h
C. Gabapentin 300mg PO q8h
D. Oxycodone 20mg PO q4h

Wound Management

Mechanism of Wound Formation

- Not well understood
- Biopsies have revealed epidermal necrosis with focal fibrin thrombi, nonspecific inflammation, and subcutaneous necrosis
- Suggested mechanisms:
  - peripheral vasoconstriction → poor perfusion and necrosis
  - small vessel disease
- Wounds appear similar to deep tissue injury



Wei, J., Wachuku, C., Berk-Krauss, J., Steele, K. T., Rosenbach, M., & Messenger, E. (2023). Severe cutaneous ulcerations secondary to xylazine (tranq): A case series. *JAAD case reports*, *36*, 89–91. https://doi.org/10.1016/j.jdcr.2023.04.016,
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Wound Progression and Phenotypes

1: At sites of injection, typically upper and lower extremities

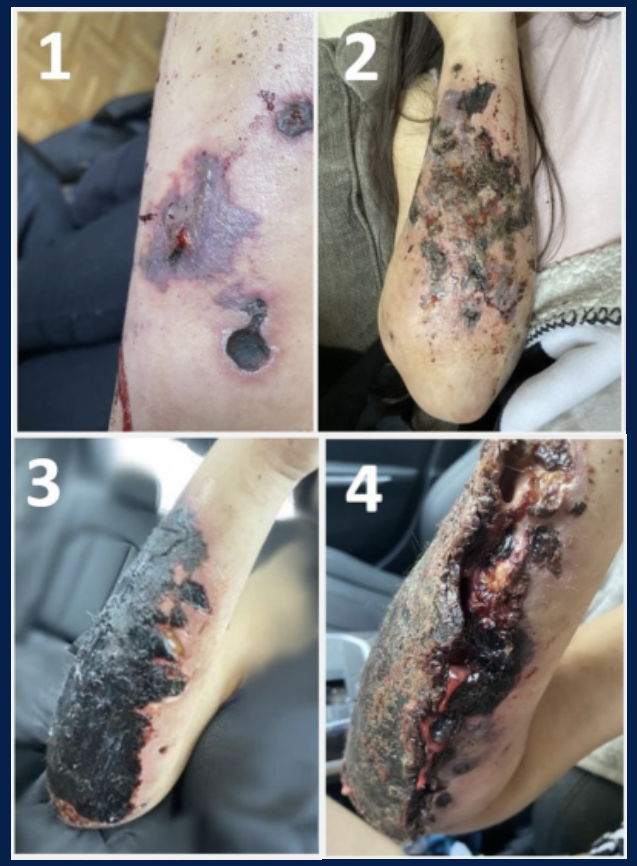
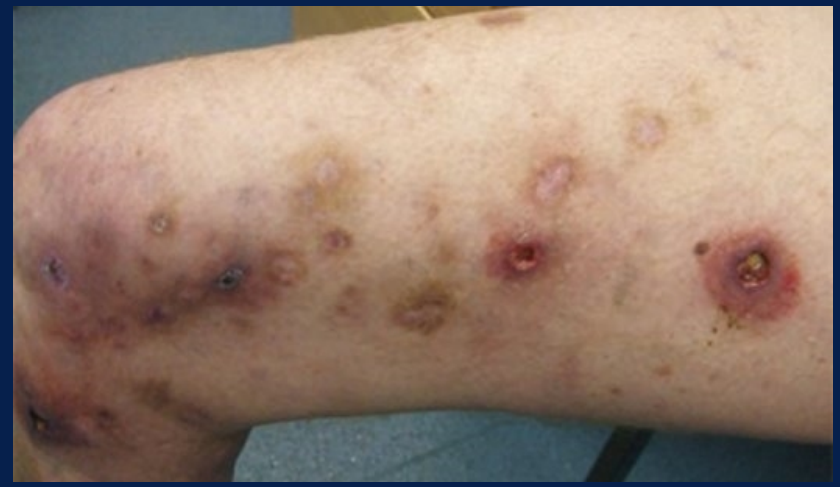


Photo Credit: Rachel McFadden

2: NOT at sites of injection, occurs in IN/smoking as well

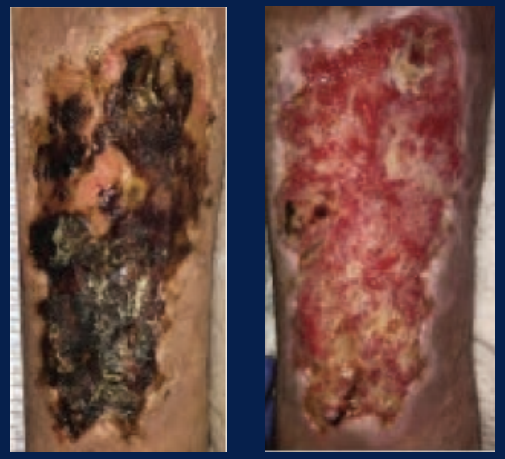


https://issuu.com/nextdistro/docs/zine_wound_care_web_110118/12

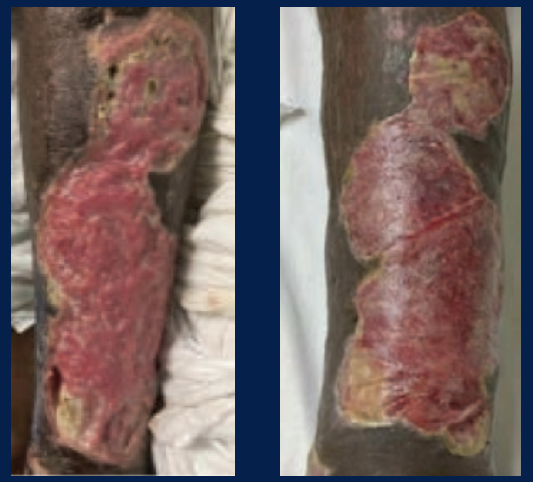
McFadden, R., Wallace-Keeshen, S., Petrillo Straub, K., Hosey, R. A., Neuschatz, R., McNulty, K., & Thakrar, A. P. (2024). Xylazine-associated Wounds: Clinical Experience From a Low-barrier Wound Care Clinic in Philadelphia. *Journal of addiction medicine, 18*(1), 9–12. https://doi.org/10.1097/ADM.0000000000001245

A Paradigm Shift in Wound Care

- Most wounds can be treated effectively with autolytic debridement and topical antibiotics
  - Systemic antibiotics only if concern for superinfection
  - Surgical debridement only if concern for deeper infection or systemic illness
- Delay or prevent progression: decrease bone and tendon involvement, prevent amputation
  - Exposed tendon or bone may benefit from placement of a dermal substitute
  - Delayed closure to allow a period of tissue healing and avoid enclosing infection
- D.I.M.E approach
  - ☐ Debridement: remove dead tissue
  - ☐ Infection/Inflammation: decrease infection risk and treat if present
  - ☐ Moisture: maintain healthy tissue
  - ☐ Edges: protect intact peri-wound tissue



The same wound after 6 days of wound care with Silvadene



Exposed tendon and visualized through BTM

McFadden, R., Wallace-Keeshen, S., Petrillo Straub, K., Hosey, R. A., Neuschatz, R., McNulty, K., & Thakrar, A. P. (2024). Xylazine-associated Wounds: Clinical Experience From a Low-barrier Wound Care Clinic in Philadelphia. *Journal of addiction medicine*, *18*(1), 9–12. https://doi.org/10.1097/ADM.0000000000001245

Temple Health. (2023). Guidelines for Xylazine-Associated Wounds. https://penncamp.org/wp-content/uploads/2024/01/Temple-Xylazine-Wounds.pdf

Wound Care Guidance

Step 1: Cleanse the Wound

NS or **Sea-clens**

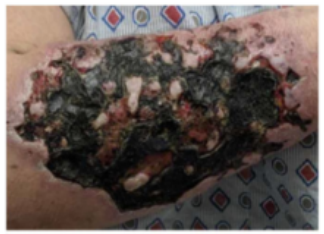
for odor and/or purulent drainage:
Dakin's 0.125%

Purpose of wound cleansing is to remove surface bacteria and debris from the wound bed.
After removing a wound dressing, the wound and surrounding skin should be gently cleansed and dried.
*Be sure to remove dressing and cleanse wound **before** assessing the wound for any odor.*

Step 2: Apply dressing

Is there a clean wound bed?

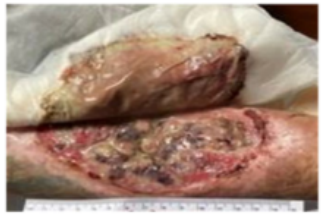
Xeroform
Cut the dressing to the wound size to prevent maceration
+ *pick 1*
Island dressing *(scant/small drainage)*
ABD and kerlix *(moderate/large drainage)*
Mepilex *(hard to dress areas)*
→ *Δ daily and prn*



Is there non-viable tissue in the wound bed? *Slough or eschar present (but no s/s infx)*
Consult wound care. Discuss with provider if general surgery should be consulted to further evaluate.

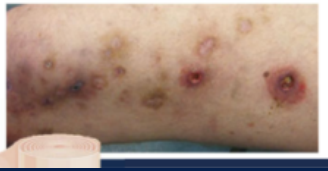
Medihoney*
Apply to wound bed
+ **Xeroform**
Cut the dressing to the wound size to prevent maceration
+ *pick 1*
Island dressing *(scant/small drainage)*
ABD and kerlix *(moderate/large drainage)*
Mepilex *(hard to dress areas)*
→ *Δ daily and prn*

Do not use* *medihoney if patient has allergy to **bees or honey. Skip medihoney, and apply xeroform + secondary dressing.*



Is there concern for infection? *S/S to look for: Purulent drainage, odor, surrounding warmth, erythema, or induration*
Consult wound care. Discuss with provider if general surgery should be consulted to further evaluate.

Dakin's 0.125% - moistened gauze
Must be ordered from pharmacy
+ *pick 1*
Island dressing *(scant/small drainage)*
ABD and kerlix *(moderate/large drainage)*
Mepilex *(hard to dress areas)*
→ *Scant/small drainage: Δ daily and prn*
Mod/large drainage: Δ q12 and prn



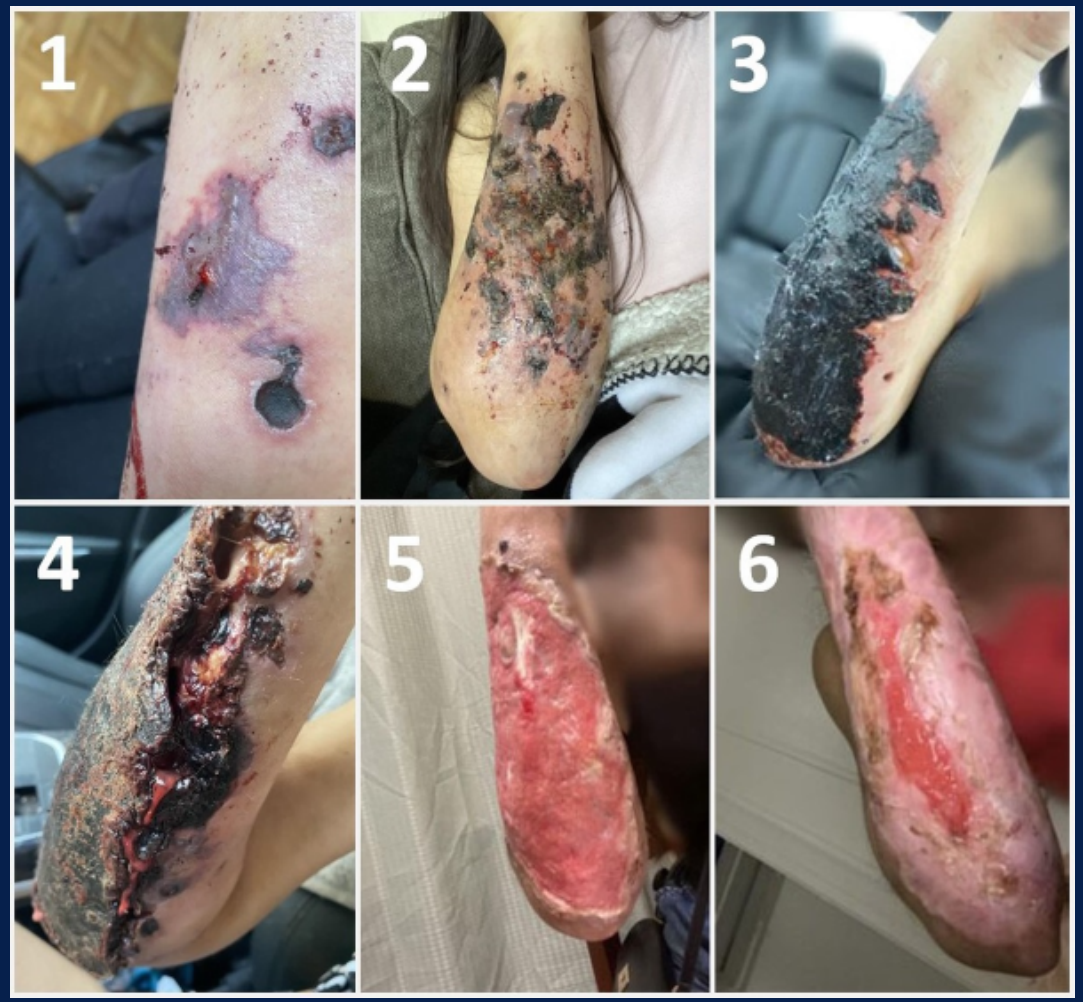
Are there multiple small wounds?

Intact scabs:	Leave ota
Superficial wounds, partial scabs:	Apply A&D, leave ota
Small wounds with drainage:	Xeroform + foam dressing, change daily
Small wounds with slough:	Medihoney + foam dressing, change daily

Pre-medicate!
Soak the dressing in NS to decrease pain
Ask the patient if they would rather remove the dressing themselves

Penn Center for Addiction Medicine and Policy. (2024). Xylazine Wounds. https://penncamp.org/clinical/xylazine-wounds/

Healing is Possible!



From wrist to elbow, her meandering pink and purple scars are a road map of being lost and found.

“People out here might think my arms look really ugly, but they aren’t familiar with tranq wounds yet,” she said. “To me, my arms look really beautiful now.”

Tracey McCann
New York Times

McFadden, R., Wallace-Keeshen, S., Petrillo Straub, K., Hosey, R. A., Neuschatz, R., McNulty, K., & Thakrar, A. P. (2024). Xylazine-associated Wounds: Clinical Experience From a Low-barrier Wound Care Clinic in Philadelphia. *Journal of addiction medicine*, *18*(1), 9–12. https://doi.org/10.1097/ADM.0000000000001245

Hoffman, J. (2023). Tranq Dope: Animal Sedative Mixed With Fentanyl Brings Fresh Horror to U.S. Drug Zones. *The New York Times.* https://www.nytimes.com/2023/01/07/health/fentanyl-xylazine-drug.html

Active substance use is not a contraindication to receiving wound care.

Pain Management

Poll: Which of the following are you utilizing for management of pain in patients with Xylazine complications?

Acute Pain

- Evaluate etiology of pain & utilize non-opioid analgesia
  - NSAIDS (ketorolac, ibuprofen)
  - High-dose acetaminophen
  - Gabapetinoids (gabapentin, lyrica)
  - Ketamine
  - Topicals (lidocaine, diclofenac)
  - Heat/ice
  - Nerve block (often contraindicated by infection)
- Address comorbid anxiety, insomnia, PTSD, social concerns

Alford, D. P., Compton, P., & Samet, J. H. (2006). Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Annals of internal medicine*, *144*(2), 127–134. https://doi.org/10.7326/0003-4819-144-2-200601170-00010

For Patients on MOUD

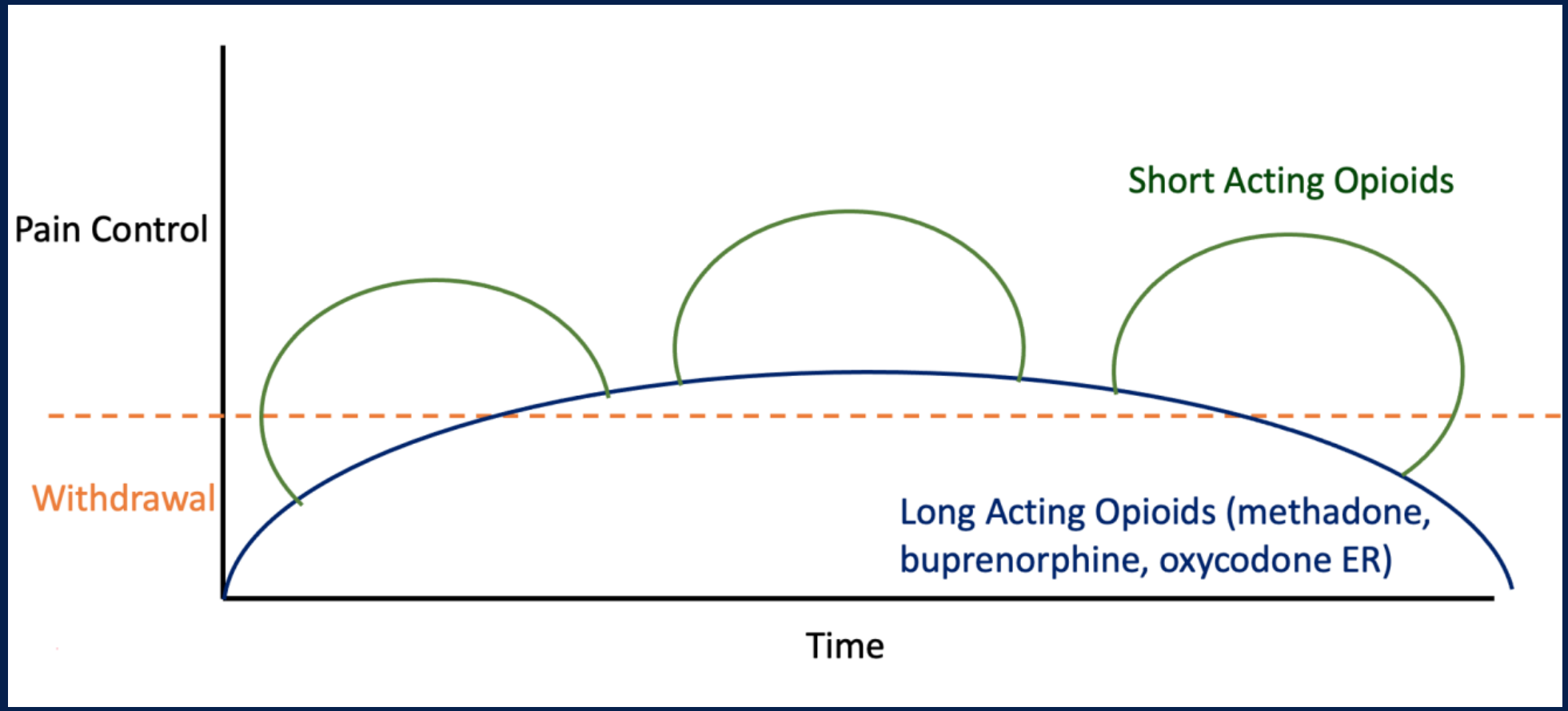
- Buprenorphine & methadone
  - Consider splitting doses to optimize analgesic regimen

Duration of Action	Methadone	Buprenorphine
Cravings/Withdrawal	Variable (24 – 36 hours)	Variable (24 – 42 hours)
Analgesia	4-8 hours	6-8 hours

Braun HM, Potee RA. (2023). Individualizing methadone treatment with split dosing: An underutilized tool. Journal of Substance Use Addiction Treatment. DOI: 10.1016/j.josat.2023.209096. PMID: 37301287

Alford AP, Compton P, Samet JH. (2006). Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Annals of Internal Medicine, 144:127-134. DOI:10.7326/0003-4819-144-2-200601170-00010. PMID:16418412

Approach to Opioid Dosing



Additional Opioid Agonists

1. Use long-acting opioid: usually methadone, buprenorphine, or oxycodone ER
2. Start a short-acting: **oxycodone 20mg q4h or hydromorphone 8mg q4h** for patients using fentanyl (oral dosing preferred) and uptitrate to effect
    - For poorly controlled pain, consider additional IV PRN (e.g. hydromorphone IV 1.5-2mg) or PCA (e.g. hydromorphone IV 0.5mg basal/0.5mg q15m bolus)
3. Use non-opioid adjuvants
4. Transition to MOUD (methadone or buprenorphine) and taper off short-acting opioids


Addiction Science & Clinical Practice

Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder

Ashish P. Thakrar[1,2*], Tanya J. Uritsky[2,3], Cara Christopher[3], Anna Winston[4], Kaitlin Ronning[5], Anna Lee Sigueza[5], Anne Caputo[5], Rachel McFadden[2,7], Jennifer M. Olenik[4], Jeanmarie Perrone[2,6], M. Kit Delgado[2,6], Margaret Lowenstein[2,4] and Peggy Compton[2,7]

- At Penn, dosing guided by expert pharmacist
- 23 high-risk patients with fentanyl dependence
- Patients received median doses 20-35mg oxycodone q4h
- No evidence of iatrogenic overdose
- 65% left on methadone/buprenorphine, self-discharge rate fell

Thakrar, A. P., Uritsky, T. J., Christopher, C., Winston, A., Ronning, K., Sigueza, A. L., Caputo, A., McFadden, R., Olenik, J. M., Perrone, J., Delgado, M. K., Lowenstein, M., & Compton, P. (2023). Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder. *Addiction science & clinical practice*, *18*(1), 13. https://doi.org/10.1186/s13722-023-00368-z

https://penncamp.org/clinical/pain-and-opioid-withdrawal-in-hospitalized-patients/

Case Continued

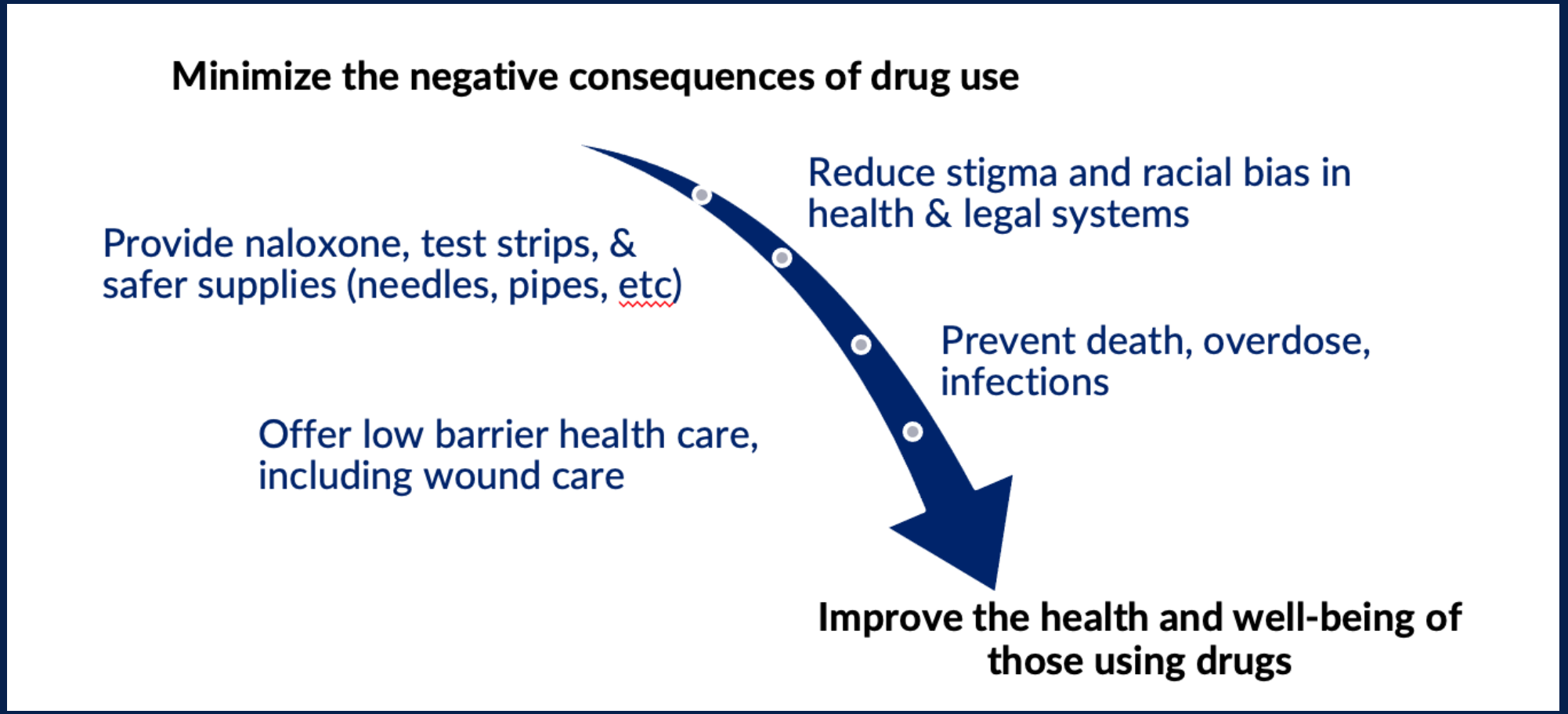
- MJ is diagnosed with bacteremia and started on IV antibiotics. She reports few withdrawal symptoms, but continues to report uncontrolled pain due to leg wounds. Her current medication regimen includes:
  - Oxycodone 40mg PO q4h, Ketamine 20mg PO q6h, methadone 80mg PO daily, acetaminophen 975mg q6h

How can we optimize MJ's pain regimen?

A. Split methadone dose (20/20/40)
B. Add ketorolac 15mg IV q6h
C. Increase ketamine 30mg PO q6h
D. Stop oxycodone

Harm Reduction

What Is Harm Reduction



Harm Reduction

- Wounds:
  - Honor patient expertise
  - Expect odor and validate emotions around it
  - Have a "go bag" with supplies ready in case patients are discharged or leave
- Identify low-barrier clinics
- Counsel patients:
  - Rotate injection sites
  - IN/smoking does not prevent wounds though they are less severe

McFadden, R., Wallace-Keeshen, S., Petrillo Straub, K., Hosey, R. A., Neuschatz, R., McNulty, K., & Thakrar, A. P. (2024). Xylazine-associated Wounds: Clinical Experience From a Low-barrier Wound Care Clinic in Philadelphia. *Journal of addiction medicine, 18*(1), 9–12. https://doi.org/10.1097/ADM.0000000000001245

Harm Reduction

- Test strips may not be very useful in xylazine "saturated" markets, but could they help PWUD avert xylazine in "emerging" markets?
  - Community drug checking and surveillance
  - Empowers PWUD to make informed choices about what they consume
- Provide test strips and explain how to use them
- Never use alone, go slow
  - Don’t forget naloxone!
  - Safe consumption sites

Reed, M. K., Imperato, N. S., Bowles, J. M., Salcedo, V. J., Guth, A., & Rising, K. L. (2022). Perspectives of people in Philadelphia who use fentanyl/heroin adulterated with the animal tranquilizer xylazine; Making a case for xylazine test strips. *Drug and alcohol dependence reports*, *4*, 100074. https://doi.org/10.1016/j.dadr.2022.100074

Case Continued

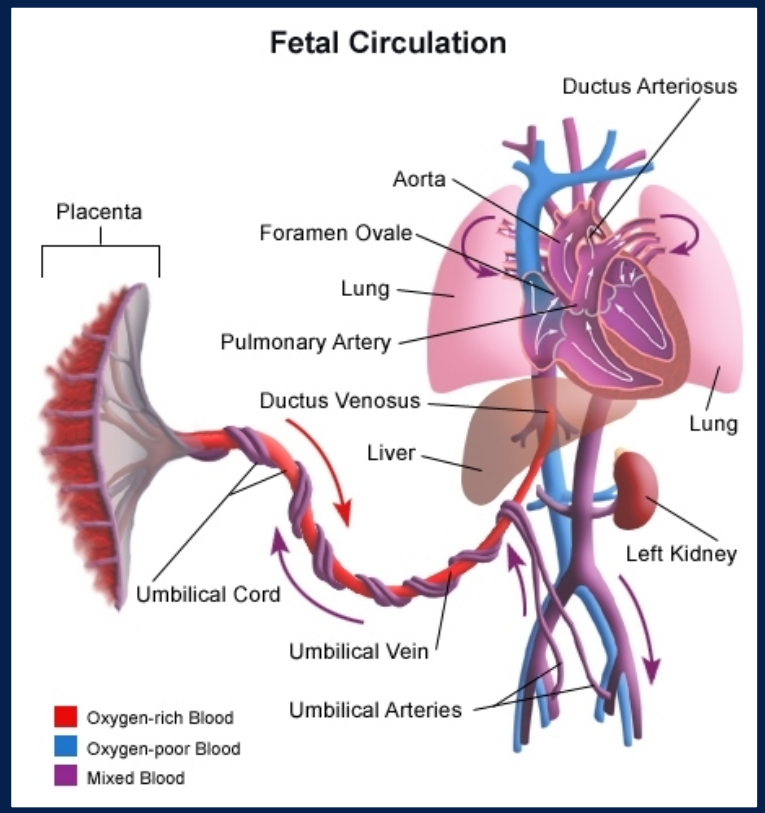
- MJ has been in the hospital receiving IV antibiotics for bacteremia for 5 days when she reports worsening anxiety, restless legs, and general irritability. Despite the team's best efforts, MJ decides she needs to leave the hospital via Patient Directed Discharge.

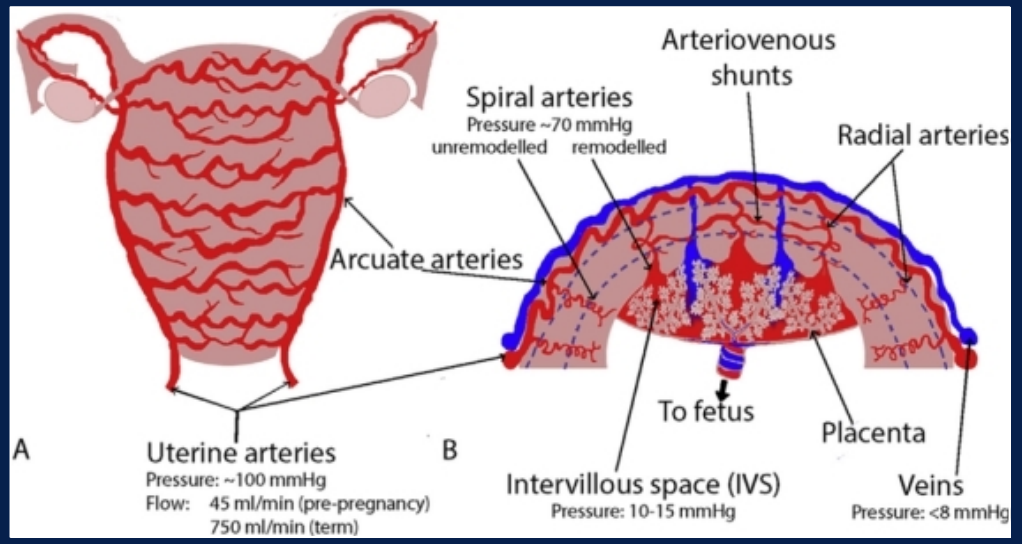
How can we make this discharge as safe as possible for MJ?

A. Prescribe oral antibiotics
B. Provide wound care supplies
C. Hand MJ Narcan on discharge
D. Connect MJ to community resources

Considerations in Pregnancy

Xylazine in Pregnancy





- Placenta carries oxygenated blood to the umbilical vein, then to the uterus
- Deoxygenated blood is carried from the fetus, to the umbilical arteries, and back to the placenta

Clark, A. R., James, J. L., Stevenson, G. N., & Collins, S. L. (2018). Understanding abnormal uterine artery Doppler waveforms: A novel computational model to explore potential causes within the utero-placental vasculature. *Placenta*, *66*, 74–81. https://doi.org/10.1016/j.placenta.2018.05.001

Stanford Medicine Children's Health - Lucile Packard Children's Hospital Stanford. (n.d.). Retrieved February 22, 2024, from https://www.stanfordchildrens.org/en/topic/default?id=fetal-circulation-90-P01790

Xylazine and Fetal Development

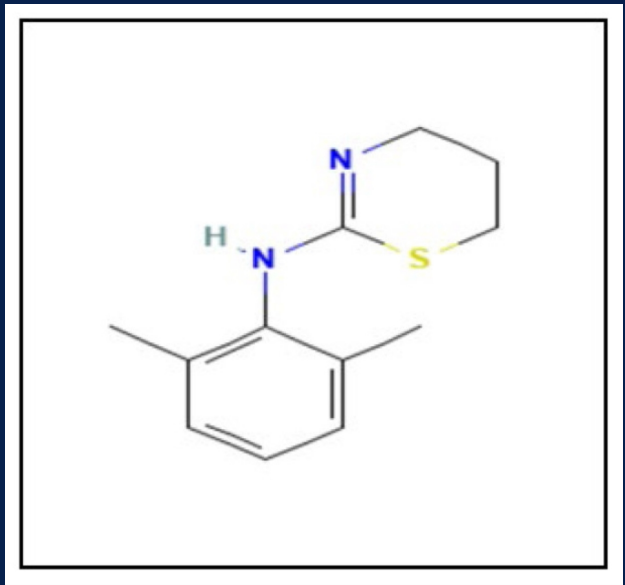


TABLE 7.2 Subtype-specific functions of α_2-AR derived from gene-targeted mouse models.—cont'd

	α_2-AR subtypes		
Physiological functions	**α_{2A}-AR**	**α_{2B}-AR**	**α_{2C}-AR**
Vasoconstriction, hypertensive effect		X	
Salt-induced hypertension		X	
Placenta angiogenesis	X	X	
Platelet aggregation		X	
Latency to attack after isolation	X		
Prevention of respiratory failure		X	
Behavior effect			
Antiepileptogenic effect	X		
Special working memory	X		
Inhibition of startle responses			X
Antianxiety	X		
Inhibition of locomotor stimulation of D-amphetamine			X
Latency to attack after isolation			X

[a]*Primary autoreceptor.*
Above data summarized in Kable et al. J Pharmacol Exp Ther 2000;293(1):1–7, Brede et al. Biol Cell 2004;96(5):343–8, and Knaus et al. Neurochem Int 2007;51(5):277–81. Also from Haubold et al. J Biol Chem 2010;285(44):34213–9.

α_2-receptors + in uterus = Increased uterine tone and decreased uterine artery blood flow

Placenta?

Umbilical artery and vein flow?

Sakamoto, H., Misumi, K., Nakama, M., & Aoki, Y. (1996). The effects of xylazine on intrauterine pressure, uterine blood flow, maternal and fetal cardiovascular and pulmonary function in pregnant goats. *The Journal of veterinary medical science*, *58*(3), 211–217. https://doi.org/10.1292/jvms.58.211

Noonan, G., & Sethi, R. (2023). Xylazine Use in Pregnancy: The Effects of the Fentanyl Adulterant Xylazine on Pregnant Patients and the Developing Fetus. *Kansas journal of medicine*, *16*, 277–279. https://doi.org/10.17161/kjm.vol16.20624

Effects of Xylazine in Pregnancy

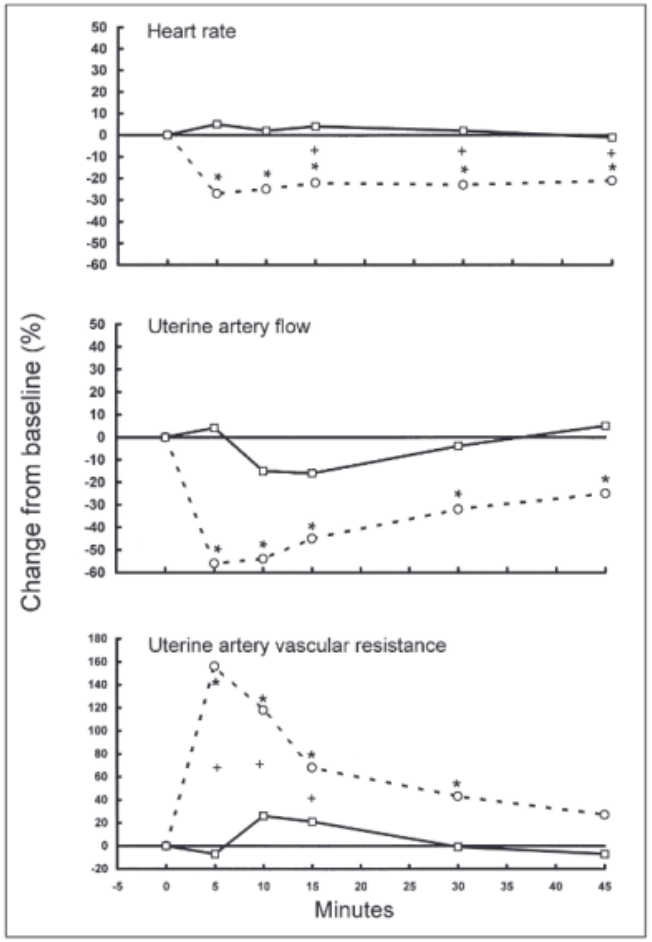


Figure 1—Percentage change in heart rate, uterine artery flow, and uterine artery vascular resistance after IV administration of xylazine (XYL; 0.04 mg/kg; open circles) or acepromazine (ACE; 0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *Value differs significantly ($P < 0.05$) from baseline value. +Value for XYL differs significantly ($P < 0.05$) from value for ACE.

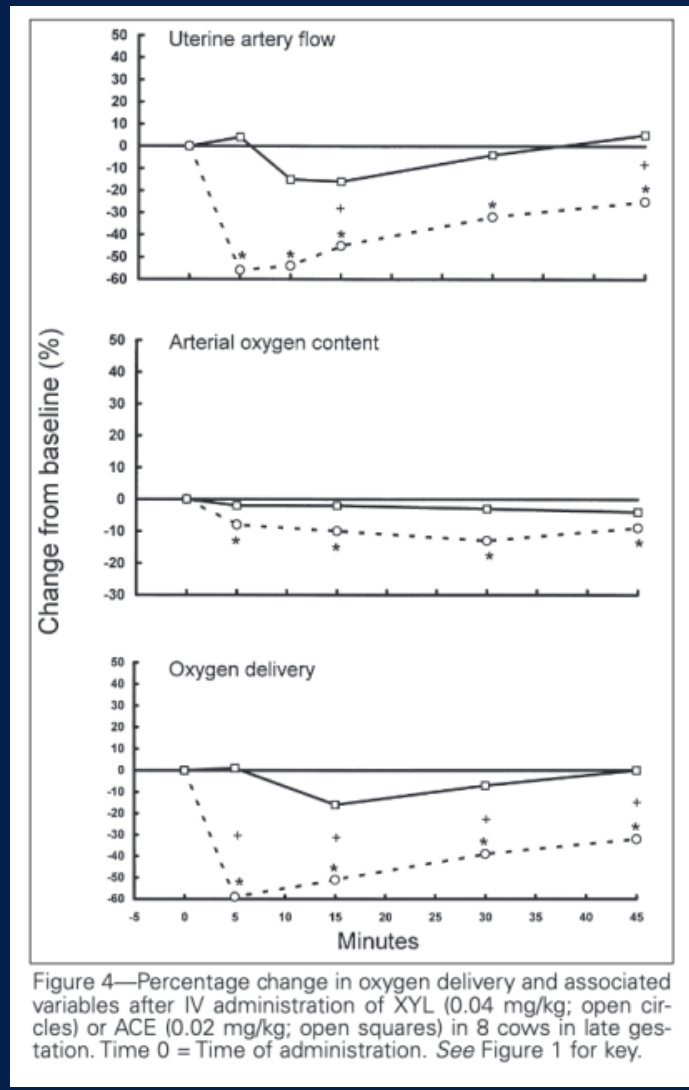


Figure 4—Percentage change in oxygen delivery and associated variables after IV administration of XYL (0.04 mg/kg; open circles) or ACE (0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *See* Figure 1 for key.

After administration of Xylazine in Cows:

- Decreased uterine blood flow
  - 59% at 5 minutes
  - 32% at 45 minutes
- Decreased oxygen delivery

May link to fetal hypoxemia and growth restriction

Hodgson, D. S., Dunlop, C. I., Chapman, P. L., & Smith, J. A. (2002). Cardiopulmonary effects of xylazine and acepromazine in pregnant cows in late gestation. *American journal of veterinary research*, *63*(12), 1695–1699. https://doi.org/10.2460/ajvr.2002.63.1695

Effects of Xylazine in Pregnancy

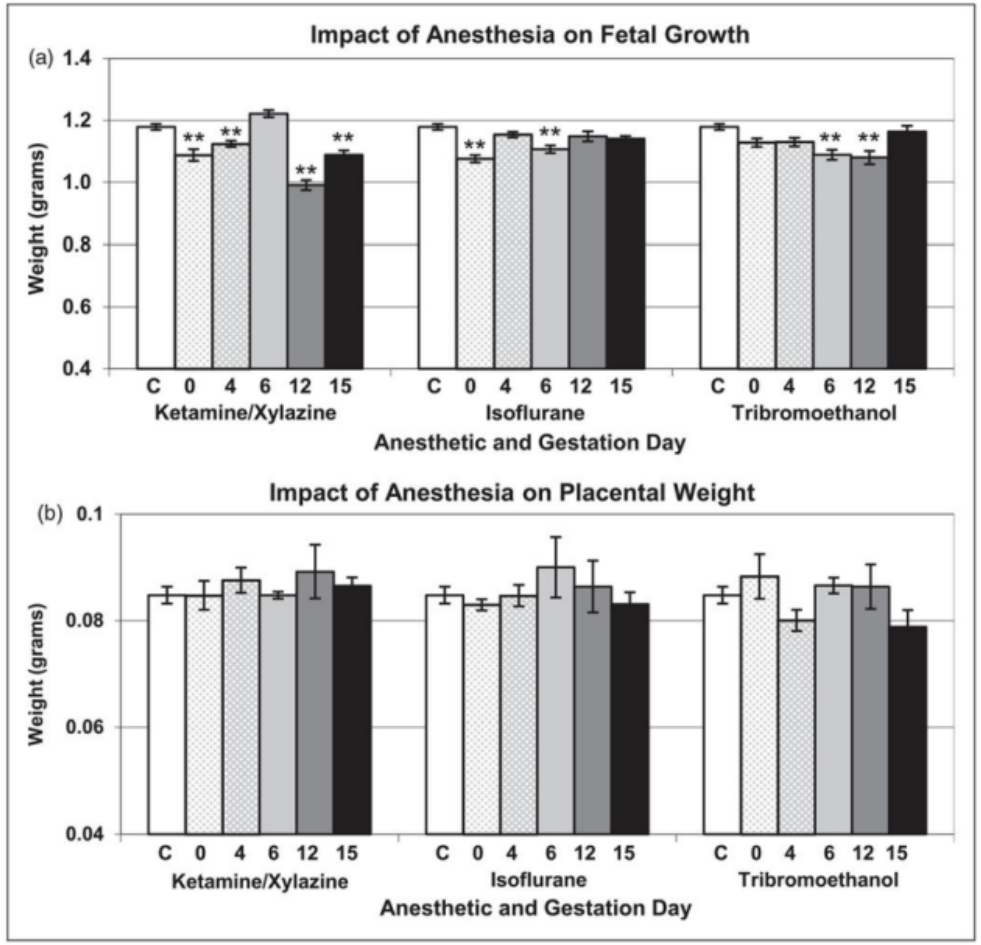


Figure 1.
Fetal weights (a) and placental weights (b) at term (E18) from pregnant mice treated with anaesthesia on the indicated gestation day. C=control group (untreated); data are presented as mean ±SEM; $^{**}P < 0.01$ compared with control mice, by analysis of variance (ANOVA).

Ketamine/Xylazine had decreased fetal growth throughout gestation

During preliminary trials, ketamine and xylazine were administered individually during growth phase:

- Xylazine was the cause of decreased fetal growth

Thaete, L. G., Levin, S. I., & Dudley, A. T. (2013). Impact of anaesthetics and analgesics on fetal growth in the mouse. *Laboratory animals*, *47*(3), 175–183. https://doi.org/10.1177/0023677213480769

Effects of Xylazine in Pregnancy

TABLE 1 Positivity of adulterants as totals and percentages (%) of total numbers of patients in total cohort, cocaine subgroup, and opiates subgroup, respectively.

Compound	Total Toxic Adulterant Positives	Positives as % of Total Patients	Cocaine Toxic Adulterant Positives	Positives as % of Cocaine Patients	Opiates Toxic Adulterant Positives	Positives as % of Opiates Patients
Caffeine	228	76%	136	74%	92	79%
Lidocaine	216	72%	138	75%	78	67%
Diphenhydramine	81	27%	55	30%	26	22%
Quetiapine	73	24%	44	24%	29	25%
Levamisole	35	12%	32	18%	3	3%
Acetaminophen	33	11%	21	12%	12	10%
Quinine	30	10%	14	8%	16	14%
Tramadol	18	6%	8	4%	10	8%
Phenacetin	15	5%	9	5%	6	5%
Dextromethorphan	8	3%	5	3%	3	3%
Promethazine	6	2%	5	3%	1	0.9%
4-Methylaminoantipyrine	3	1%	0	0%	3	3%
Xylazine	3	1%	0	0%	3	3%
4-Formylaminoantipyrine	2	0.7%	1	0.5%	1	0.9%
Ketamine	2	0.7%	1	0.5%	1	0.9%
Aminopyrine	1	0.3%	0	0%	1	0.9%
4-Aminoantipyrine	1	0.3%	0	0%	1	0.9%
Procaine	1	0.3%	0	0%	1	0.9%
Noxiptiline	1	0.3%	1	0.5%	0	0%
Benzocaine	0	0%	0	0%	0	0%
Diltiazem	0	0%	0	0%	0	0%
Total (Patients)	300		183		117	

Midthun, K. M., Nelson, B. N., Strathmann, F. G., Browne, T., & Logan, B. K. (2023). Analysis of umbilical cord tissue as an indicator of *in utero* exposure to toxic adulterating substances. *Frontiers in pediatrics*, *11*, 1127020. https://doi.org/10.3389/fped.2023.1127020

Effects of Xylazine in Pregnancy- Summary

- Many theorized effects, some data in animal studies
  - Decreased uterine artery blood flow, increased resistance, hypoxemia
    - ? Growth restriction, cerebral palsy, organogenesis dysregulation, miscarriage

- Unknown effects on:
  - Placenta
  - Uterine arteries and veins
  - Fetal α2 receptor regulated development

Medications: Pregnancy & Lactation

Medication	Pregnancy	Use	Lactation	Use
Clonidine	Crosses placenta	Caution	4.1-8.4% Galactorrhea. Sedation, hypoglycemia.	Caution
Gabapentin	Crosses placenta, folic acid	Caution	1.3-3.8%	OK
Olanzapine	Crosses placenta, fetal extrapyramidal and withdrawal risk	Caution	0-2.66% Somnolence, irritability, tremor, insomnia	OK
Hydroxyzine	Crosses placenta, fetal withdrawal	AVOID in 1st Trimester	Minimal levels. Sedation, irritability. Decreased milk supply	OK
Ketamine	Crosses placenta, fetal brain development	AVOID	Unclear levels	AVOID
Dexmedetomidine	Crosses placenta, fetal bradycardia	Caution	0.04-0.098%	OK
Phenobarbital	Crosses placenta, congenital effects, fetal withdrawal	AVOID	72.5% Sedation and withdrawal seizures, avoid	AVOID

Drugs and Lactation Database(LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Retrieved February 22, 2022, from https://www.ncbi.nlm.nih.gov/books/NBK501922/

Case Continued

- MJ re-presents to the ED 1 week after PDD. She reports experiencing fevers, chills, body aches, and vomiting. She has not used in 2 days because she has felt so unwell.
- In the ED
  - T 101.1 | BP 115/93 mmHg | HR 102 | HCG +

How can we treat MJ's withdrawal symptoms?

A. Re-start methadone + full agonists
B. Phenobarbital 64.8mg q6h
C. Start clonidine 0.1mg q8h
D. Start ketamine 20mg PO q6h

Small-Group Case
Share your Learning!

Final Takeaways

- Xylazine prevalence is increasing; primarily in the NE but also nationally
- Xylazine has been found in dope, but also stimulants
  - Treat overdoses with naloxone because most are mixed opioid and xylazine
- Primarily an α-2 adrenergic agonist
- Withdrawal syndrome: primarily restlessness and anxiety, overlapping with opioid withdrawal
  - Treat with clonidine, ketamine, gabapentin, olanzapine, phenobarbital, benzodiazepines
- Wounds are worst at injection site, but also seen at other sites and with IN/smoking
- Wound care is focused on maintaining healthy tissue, debriding dead tissue, preventing infection and progression to tendon/bone involvement and limb loss
- Wounds are very painful; treat using multimodal analgesia + MOUD
- Xylazine may decrease uterine artery blood flow and cause growth restriction, cerebral palsy, organogenesis dysregulation, miscarriage

www.PennCAMP.org

Questions & Discussion

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