Precipitated Withdrawal 2.0: Outpatient Tips and Tricks

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Learning Objectives

- Identify patient characteristics or substance use patterns that predict increased risk for precipitated withdrawal
- Compare buprenorphine induction protocols - micro/low dosing with sublingual or transdermal formulations, and macrodosing to avoid precipitated withdrawal
- Review the existing evidence for management of precipitated opioid withdrawal

Case 1

- 40 y.o. female with no significant medical problems presenting to your outpatient clinic with history of daily heroin use
  - Requesting treatment with buprenorphine-naloxone
- Daily heroin use IV for the past year
- Last use 24 hours ago
- Uses methamphetamine 2-3x per week
  - Last use 24 hours ago
- Clinical opioid withdrawal score (COWS) 6

Case 1

- She was given an initial dose of 8mg-2mg sublingual buprenorphine-naloxone
  - Within 30 minutes developed:
    - Loose stools, runny nose, muscle twitching, anxiety, diaphoresis
    - Hypertension, tachycardia

Case 1: Panel Questions

- What factors may contribute to increased risk of precipitated withdrawal?
- Would you have chosen this induction protocol?
  - What factors do you consider when choosing induction protocol?

Audience Poll

- For your last 5 inductions, what technique did you most commonly use for initiation?

  a. Normal induction

  b. Micro/low dose induction

  c. Macro-induction

  d. I don't know what any of these terms mean

Examples: Outpatient Micro/Low-Induction/Cross Taper: Three day

	Dosing Schedule	Total Daily Dose Bup.	Opioid Use
Day 1	0.5 mg buprenorphine q3 hours x 2 1 mg buprenorphine q3 hours x 2 2 mg buprenorphine q3 hours x 2	7 mg	+/-
Day 2	8-12mg	8-12mg	Stop full opioid agonist
Day 3	Goal dose 12-16 mg		

Slide Courtesy of Dr. Brian Grahan

Examples: Outpatient Low Dose Induction

- Stop full opioid agonist
- Day 1: 1mg/0.25 SL bup/nlx tid-qid
- Day 2: 2mg/0.5 SL bup/nlx tid-qid
- Day 3: 4mg/1mg SL bup/nlx bid
- Day 4: 8mg/2mg-12mg/1.5mg SL bup/nlx daily (or bid)

Case 1: Panel Questions

- Have you used other formulations of buprenorphine for induction In the outpatient setting?
- Is there a higher risk of precipitated withdrawal with different formulations?

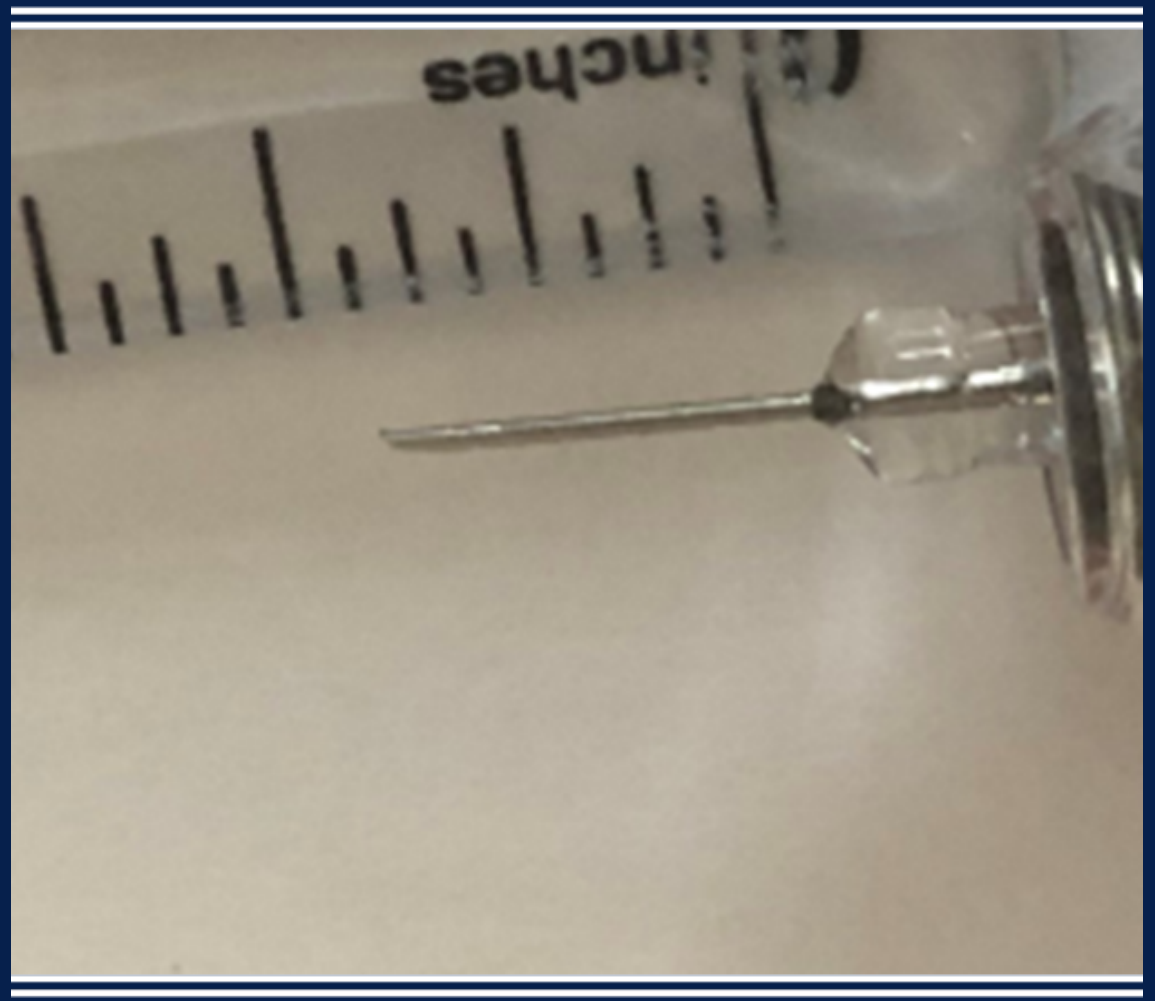
Examples: Transdermal Patch Induction

	Dosing Schedule	Total Daily Dose Bup	Opioid Use
Day 1	#1 20 mcg bup transdermal patch	0.5 mg	+/-
Day 2	Place 2nd 20 mcg bup transdermal patch	1 mg	Decrease full opioid agonist
Day 3	Place 3rd 20 mcg bup transdermal patch	1.5 mg	Decrease full opioid agonist
Day 4	Remove #3 bup transdermal patch Start 2-8 mg sublingual buprenorphine	2 mg-8 mg	Stop full opioid agonist

Ghosh et al, 2019

XR Buprenorphine: CAM2038

- 7day duration SQ injection
- Can be administered even with low COWS 4-8
- Overcomes early treatment ambivalence
- Mitigates diversion concerns



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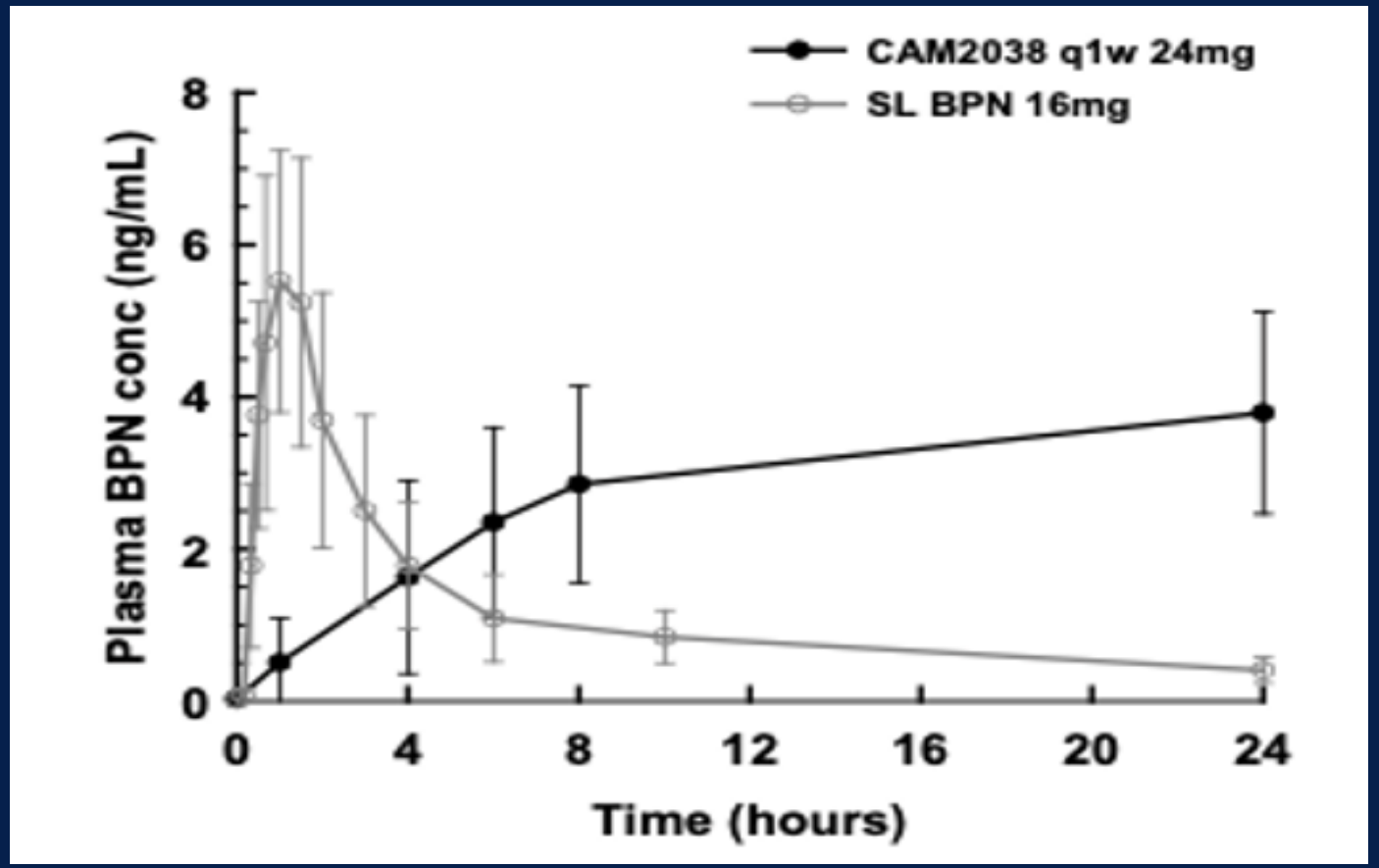
ED-INitiated BupreNOrphine VAlidaTION Network Trial ED INNOVATION



Pharmacokinetics of XR- & SL- Buprenorphine

Case 1

- Pt with daily heroin use, given 8mg-2mg buprenorphine naloxone in the clinic→ precipitated withdrawal

Audience Poll

- What resources do you have for monitoring and treating precipitated withdrawal?
  - Access to buprenorphine products
  - Access to adjunct agents
  - Room availability
  - Nursing staff
  - Medical providers
  - Time
  - Other _____

Case 1: Panel Questions

- How would you manage this patient's precipitated withdrawal in the outpatient setting?

Adjunct Agents

TABLE 1. ADJUNCTIVE THERAPY - Consider if symptoms persist after maximum dose of buprenorphine given	
General withdrawal symptoms	Clonidine 0.1 mg PO Q4H PRN (hold for SBP < 90 mmHg) (Max total dose=0.3 mg) Hydroxyzine 25 mg PO Q8H PRN Lorazepam 1 mg PO/IM Q1H PRN (caution beyond 2 doses)
Nausea and vomiting	Ondansetron 4 mg ODT/IV Q4H PRN
Diarrhea	Loperamide 4 mg PO, then 2 mg PO Q2H PRN (max total dose = 8 mg)
Myalgias and arthralgias	Ibuprofen 600 mg PO Q6H PRN

Summary of Methods for Management Precipitated Withdrawal

- Giving total 24-32mg buprenorphine to provide enough agonist effect from buprenorphine to suppress the withdrawal
  - Giving in 16mg doses?

  or
- 2mg/0.5mg buprenorphine-naloxone q1hr for several doses. Followed by 8mg-2mg for one to two doses.

  or
- Stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day

+/- adjunct agents

Case 1

- For precipitated withdrawal symptoms→ given an additional 16mg-2mg dose of sublingual buprenorphine-naloxone
- Despite this: ongoing symptoms of precipitated withdrawal
  - Next,
    - 0.1 mg clonidine
    - 4 mg ondansetron
    - 60 mg ketorolac
- Still, ongoing symptoms remain
  - COWS 19-23

Case 1: Panel Questions

- How can telemedicine be of benefit for management of outpatient precipitated withdrawal?
- What are indications you would consider for transfer for higher level of care?

Case Follow up

- Given another 8 mg-2 mg buprenorphine-naloxone in the clinic
- Due to ongoing symptoms after 32mg-8mg buprenorphine-naloxone the patient was brought to the emergency department
  - Vital Signs: 180 MHg/100 mm Hg, 105 bpm
  - COWS 19 (moderate withdrawal)
- Given:
  - 10 mg IV olanzapine
  - Additional 16 mg buprenorphine–naloxone sublingual attempted, however partially spit out some of the tabs
    - Minimal improvement
  - 10 mg IV olanzapine
    - Continued to be restless
  - 25mg ketamine x 3
  - Patient requested to be discharged from the emergency department with no further medications
- Patient later found to have two bottles of methadone in their belongings at the clinic

Final Takeaways/Summary

- A variety of induction protocols exist for induction with buprenorphine-naloxone including micro/low dosing with sublingual formulations, strategies aimed at changing bioavailability, transdermal patch use, macrodosing, or subcutaneous buprenorphine
- Risk of precipitated withdrawal varies with induction strategy and patient history, and possibly with use of methadone or fentanyl
- Uncomplicated precipitated opioid withdrawal can be managed in the outpatient setting if there are adequate resources available

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CME Questions

- What is an example of a “low” induction dose for buprenorphine?
  16 milligrams; 1 milligram ;32 milligrams ; 8 Milligrams

- At what dose of buprenorphine is there thought to be 50% opioid receptor saturation?
  2 to 4 milligrams; 1 milligram ;12 milligrams ; 32 milligrams

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- Does fentanyl have a higher or lower binding affinity than buprenorphine to mu opioid receptors
  Higher; **lower;** the same ; fentanyl does not bind to mu opioid receptors

- The Ki for buprenorphine=0.2157 nM,Fentanyl Ki is 1.346 nM. The ki is inverse to the binding affinity

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