PCSS Providers Clinical Support System

Challenging Inductions

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Disclosures

- No disclosures
- No conflicts of interest

The content of this activity may include discussion of off label or investigative drug uses.
The faculty is aware that is their responsibility to disclose this information.

Target Audience

- The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.

- The Fundamentals of Addiction Medicine ECHO (FAME) series is for physicians, physician assistants, nurse practitioners, nurses, and behavioral health specialists. It is designed for those new to treating patients with addiction and for individuals who have had little or no addiction training.

Educational Objectives

At the conclusion of this activity participants should be able to:

1. Describe the challenges with buprenorphine initiation in the era of fentanyl
2. Formulate a plan to pre-empt withdrawal with the use of non-opioid withdrawal medications
3. Use low-dose initiation for patients with a history of precipitated withdrawal
4. Apply shared decision-making to select an approach to buprenorphine initiation for specific patients

Outline

- **I. Challenging buprenorphine inductions**
  - **What's going on?**

    Precipitated & protracted withdrawal for a minority of patients
  - **What can we do about it?**

    1. Preempt opioid withdrawal
    2. Low-dose initiation (alternative to traditional initiation)
    3. "High-dose" induction (modification to traditional initiation)
    4. Treat precipitated opioid withdrawal
    5. Patient selection & counseling
- **II. Challenging methadone inductions**

  A brief overview

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What's going on?
Precipitated & protracted withdrawal

Patient reports

Research Paper

"Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl

A: Yes, for me it sends me into precipitated withdrawals every fucking time that I try to get off of fentanyl. Then I have these Sub doctors telling me that it's not real and it's like, go fucking ask the people that are buying it off the streets. It is real! I waited 80 hours. I

Silverstein, et al. *Int J Drug Policy* (2019)

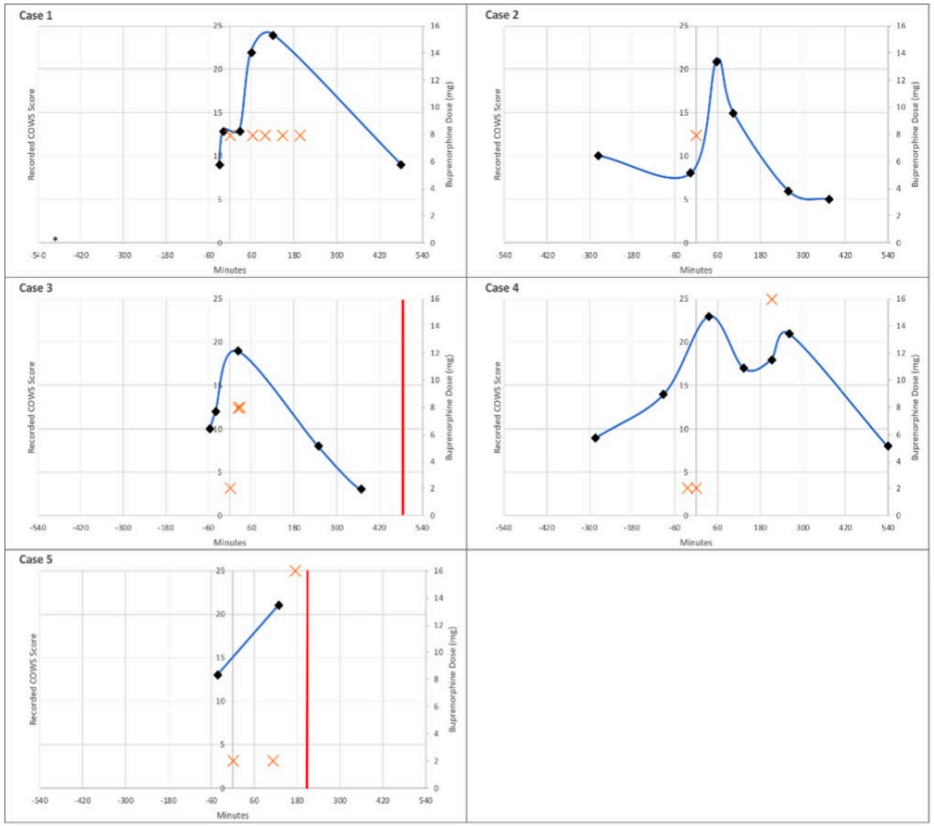
A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

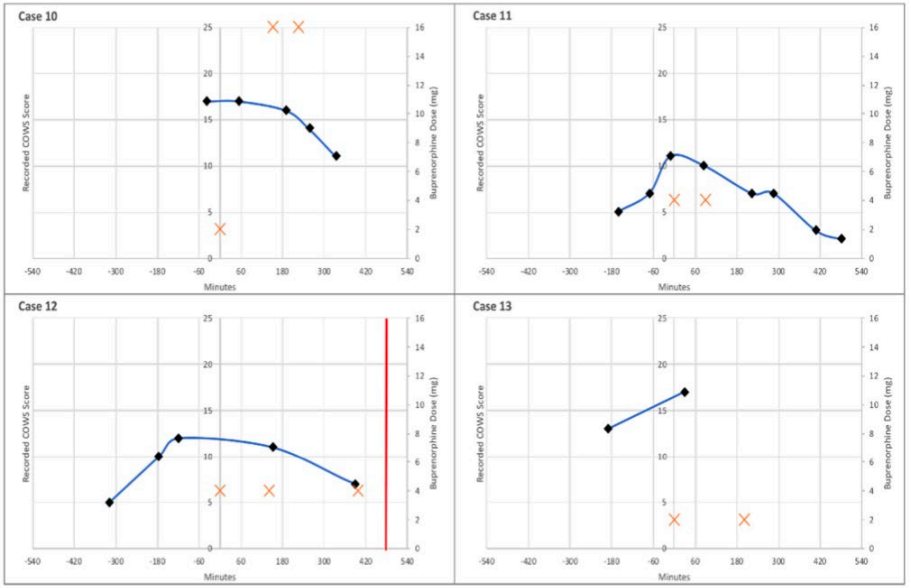
What's going on?
Precipitated & protracted withdrawal

Clinical evidence

Precipitated withdrawal



Protracted withdrawal



Spadaro, *JACEP Open* (2023)

What's going on?
Precipitated & protracted withdrawal

How often is this happening?

Low Incidence of Precipitated Withdrawal in Emergency Department-Initiated Buprenorphine, Despite High Prevalence of Fentanyl Use

Gail D'Onofrio[1], Jeanmarie Perrone[2], Andrew A. Herring[3], Kathryn Hawk[4], Ryan P. McCormack[5], Ethan Cowan[6], Michelle R. Lofwall[7], Sharon L. Walsh[8], Shara Martel[9], Patricia Owens[10], Kristin Huntley, James Dzuira[11], Abigail G. Matthews[12], David A. Fiellin[11]

Among 800 enrolled in an ED trial (76% fentanyl+)…
1% experienced PW

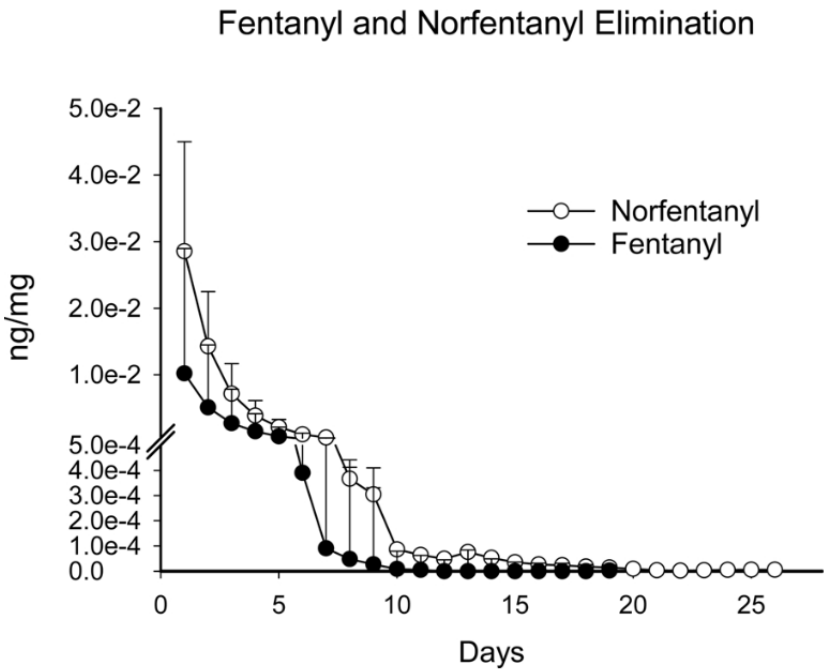
Evidence of Buprenorphine-precipitated Withdrawal in Persons Who Use Fentanyl

Neil B. Varshneya, PhD, Ashish P. Thakrar, MD, J. Gregory Hobelmann, MD, Kelly E. Dunn, PhD, MBA, and Andrew S. Huhn, PhD, MBA

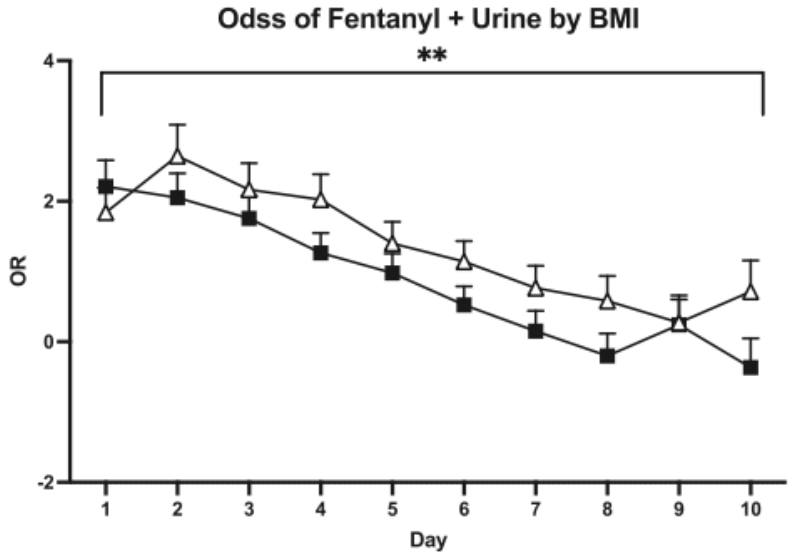
Among 685 who reported experience with buprenorphine after fentanyl…
36.5% reported severe opioid withdrawal

What's going on?
Precipitated & protracted withdrawal

Why is this happening?



Huhn, *Drug & Alcohol Dependence (2020)*



Luba, *Addiction* (2022)

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What can we do about it?
1. Preempt opioid withdrawal

Use non-opioids for withdrawal management

- With heroin or oxycodone, we could be confident that buprenorphine would relieve opioid withdrawal after 8 hours of abstinence
- Now, we should preempt opioid withdrawal symptoms that might worsen or persist. Pick ones that matter most to the patient:
  - *Lofexidine (0.54mg q6h) vs. Clonidine (0.1mg q6-8h)*
  - *Ondansetron (4-8mg q6-8h)*
  - *Loperamide (2-4mg q6-12h)*
  - *Others: dicyclomine, acetaminophen, NSAIDs*

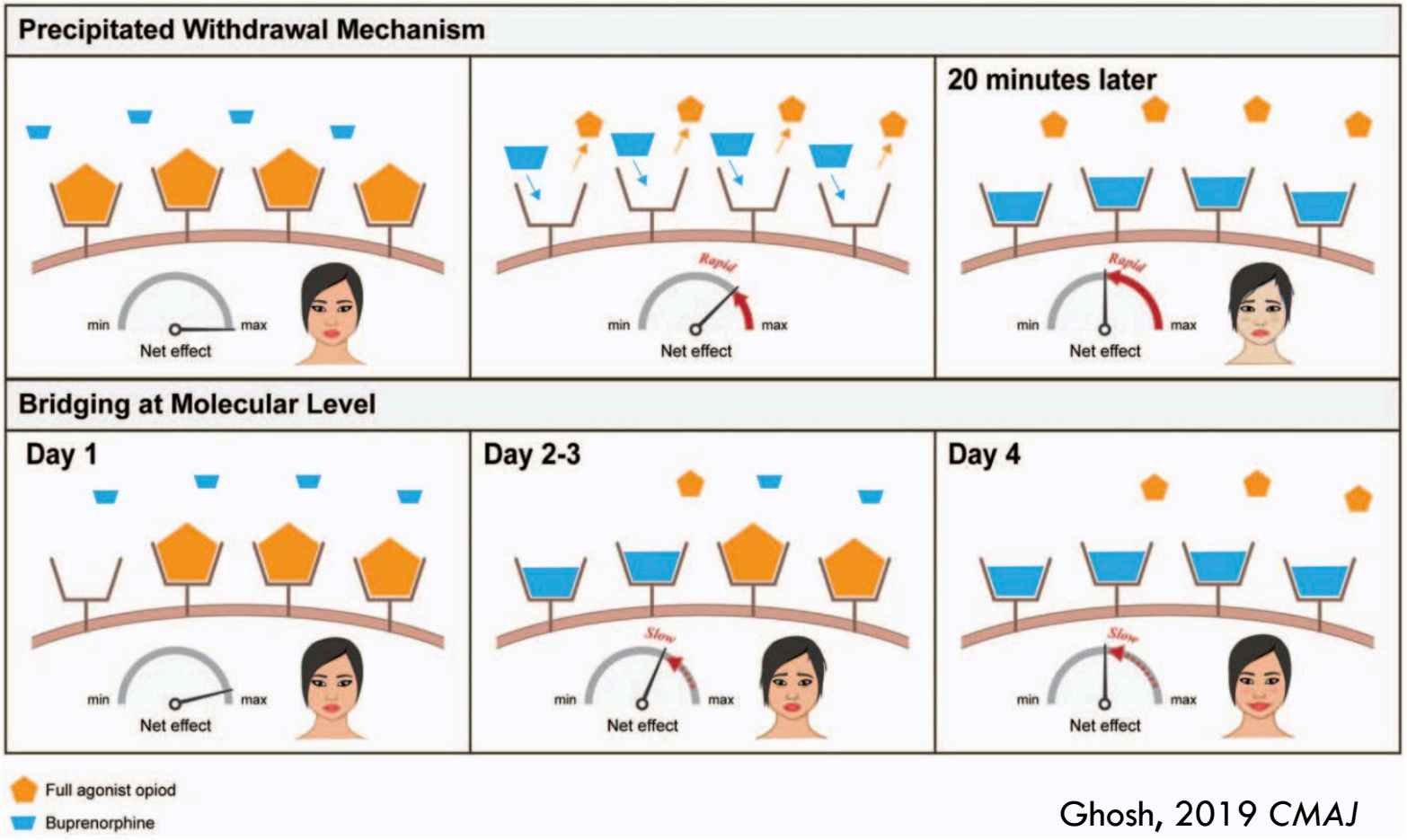
What can we do about it?
2. Low-dose initiation ("Microdosing")

Definition: Administering small and gradually increasing doses of buprenorphine while continuing or tapering a full-agonist opioid over 2-7 days.

Goal: Start buprenorphine without requiring or precipitating withdrawal

- Initial doses: ~0.5mg sublingual (or equivalent)
- Various buprenorphine formulations have been used:
  - Sublingual films or tablets
  - Transdermal patch
  - Buccal film
  - Intravenous

What can we do about it?
2. Low-dose initiation



Ghosh, 2019 *CMAJ*

What can we do about it?
2. Low-dose initiation

Common elements

1. Starting dose: **most commonly ≤0.5mg SL** (or equivalent)
2. Maintain full-agonist opioid throughout transition
3. Slowly escalate buprenorphine over 16h – 6 days:

   Eg. 0.5mg x4, 1mg x 2, 2mg x2 q6h, then 8-12mg BID
4. Once ≥8mg SL buprenorphine, ok to rapidly taper off full-agonist opioid

Ghosh CMAJ (2019); Cohen J Add Med (2021)

Specific Approaches to Low-Dose Initiation

- **Inpatient full-agonist opioid:** No limitations to administering
- **Outpatient full-agonist opioid:** Instruct patient to continue using

Formulation	Setting	Doses	Timing	Notes
Intravenous[1] (Buprenex)	Inpatient	0.15mg x2-4, 0.3mg x2, 0.6mg x1-2, then SL	q4-6h	Rapid onset & titration, need IV access
Transdermal patch[2] (Butrans)	Inpatient (mostly)	20 mcg patch x1d, then SL (e.g. 1mg q3-6h)	Daily	Hard to obtain in outpatient settings
Buccal film[3] (Belbuca)	Inpatient (mostly)	225 mcg x2-4, 450 mcg x2, then SL (start at 2mg)	q3-6h	Hard to obtain in outpatient settings
SL films/tabs[4]	Outpatient (mostly)	**0.5mg SL** x2-4, 1mg x 2, 2mg x1-2, 4mg x1,, then full dose (8-12mg)	q2-24h	Concern about stability when splitting films/tabs

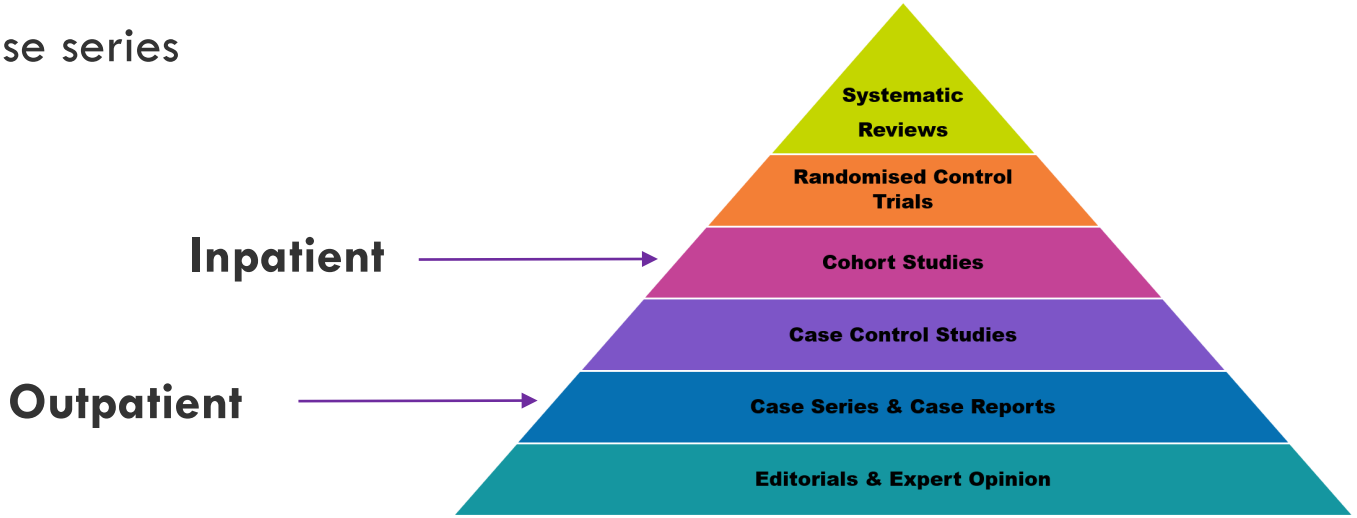
Note: slide adapted from workshop for AMERSA 2021

[1]Jablonski Dr Alc Dep (2022), [2]Sokolski J Add Med (2023), [3]Weimer J Add Med (2021), [4]Cohen J Add Med (2021)

Evidence for Low-Dose Initiation

Evidence base:

- 3 **inpatient** retrospective cohort analyses (~180 cases)
- 25+ **inpatient** case studies/series (~120 cases)
- A few **outpatient** case series



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What can we do about it?
"High-dose" initiation

Definition: Rapidly titrating buprenorphine to therapeutic doses (often 24-32mg) within 2-24hr

- **Goal: achieve therapeutic doses faster for patients who start buprenorphine in withdrawal** (eg. in Emergency Department settings)
- Titrating doses >12mg in first 24hrs appears to be safe for patients with fentanyl dependence (Herring, JAMA Netw Open 2021)
- Exploratory: using for patients with recent naloxone overdose
  - Start therapeutic buprenorphine without worsening withdrawal (?)

NOTE: Only consider for patients who already have withdrawal. No evidence of safety or efficacy with this approach in patients BEFORE withdrawal starts.

What can we do about it?
Treat precipitated withdrawal

How do we treat precipitated withdrawal?

1. Give more buprenorphine
   - Very little evidence, but case reports and expert guidance suggests this might help (Oakley, Dr Alc Rev 2021; Quattlebaum, Fam Pract 2021)
   - Unlikely to make it worse; might reduce the length of withdrawal
   - Alternative: Hold buprenorphine initiation for 24 hours and treat opioid withdrawal using full-agonist opioids
2. Use non-opioid adjuvants liberally
   - Recent research has described ketamine, benzodiazepines, and other non-traditional pharmacotherapy

What can we do about it?
Patient Selection & Counseling

Shared decision-making about goals, risks, and state of evidence

- Elicit prior experience with buprenorphine
  - Especially important to **review any precipitated withdrawal events.** "*What happened? How could this be avoided in the future?*"
- Explain your local protocols
- Discuss any adaptations that might be available
- Together, make a plan about next steps
- Check in regularly about the progress of your original plan and make any needed adaptations
  - Often requires daily calls in outpatient settings

Note: slide adapted from workshop for AMERSA 2021

What can we do about it?
Patient Selection & Counseling

Shared decision-making about goals, risks, and state of evidence

My approach…

- **Outpatient approach <u>for most</u>:**
  - Traditional initiation (wait >12-24hrs from last use)
  - Achieve therapeutic doses (~8-12mg BID) within 12 hours
  - Liberal use of co-prescribed, non-opioid withdrawal adjuvants
- **For patients with a <u>history of precipitated withdrawal</u>, who <u>require ongoing short-acting opioids</u> (eg. post-op), or who <u>cannot tolerate any withdrawal</u>:**
  - Low-dose initiation
    - Simplify, simplify, simplify
    - Close contact (daily conversations)
    - Harm reduction during period of ongoing use

Challenging Buprenorphine Inductions
A Summary

What can we do about precipitated or protracted withdrawal?

1. Preempt opioid withdrawal
   - Co-prescribe non-opioid adjuvants with bup starts
2. Low-dose initiation (alternative to traditional initiation)
   - A promising approach for some patients
3. "High-dose" induction (modification to traditional initiation)
   - Safe to titrate bup to therapeutic doses within 12 hours
4. Treat precipitated opioid withdrawal
   - Give more bup, use non-opioid adjuvants (low level evidence)
5. Patient selection & counseling
   - Shared decision-making, but generally start with traditional approach for most patients

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Challenging Methadone Initiations

- Fentanyl is potent: 25-50x as strong as heroin (diacetylmorphine)
- All methadone initiation research was conducted before the fentanyl era and in outpatient settings
- Traditional approaches to dosing and initiation appear to be insufficient for patients – most continue using during the initial dose titration period (weeks!)
- Novel approaches: increase by 10mg/day up to 50-60mg, others…

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journal homepage: www.elsevier.com/locate/jsat

Adapting methadone inductions to the fentanyl era

Buresh et al., 2022

References (1)

American Society of Addiction Medicine. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. *Journal of Addiction Medicine*. 2020;14(2S):1-91. doi:10.1097/ADM.0000000000000633

Antoine D, Huhn AS, Strain EC, et al. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. *The American Journal on Addictions*. 2020;n/a(n/a). doi:10.1111/ajad.13069

Buresh M, Nahvi S, Steiger S, Weinstein ZM. Adapting methadone inductions to the fentanyl era. *Journal of Substance Abuse Treatment*. Published online June 2022:108832. doi:10.1016/j.jsat.2022.108832

Cohen SM, Weimer MB, Levander XA, Peckham AM, Tetrault JM, Morford KL. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. *Journal of Addiction Medicine*. 2021;Publish Ahead of Print. doi:10.1097/ADM.0000000000000945

Ghosh SM, Klaire S, Tanguay R, Manek M, Azar P. A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings: *The Canadian Journal of Addiction*. 2019;10(4):41-50. doi:10.1097/CXA.0000000000000072

Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug and Alcohol Dependence*. 2020;214:108147. doi:10.1016/j.drugalcdep.2020.108147

References (2)

Jablonski LA, Bodnar AR, Stewart RW. Development of an intravenous low-dose buprenorphine initiation protocol. *Drug Alcohol Depend*. 2022;237:109541. doi:10.1016/j.drugalcdep.2022.109541

Luba R, Jones J, Choi CJ, Comer S. Fentanyl withdrawal: Understanding symptom severity and exploring the role of body mass index on withdrawal symptoms and clearance. *Addiction*. Published online December 13, 2022:add.16100. doi:10.1111/add.16100

Oakley B, Wilson H, Hayes V, Lintzeris N. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. *Drug Alcohol Rev*. 2021;40(4):567-571. doi:10.1111/dar.13228

Quattlebaum THN, Kiyokawa M, Murata KA. A case of buprenorphine-precipitated withdrawal managed with high-dose buprenorphine. *Family Practice*. Published online June 26, 2021:cmab073. doi:10.1093/fampra/cmab073

SAEM22 Abstracts. *Academic Emergency Medicine*. 2022;29(S1):S8-S429. doi:10.1111/acem.14511

References (3)

Shearer D, Young S, Fairbairn N, Brar R. Challenges with buprenorphine inductions in the context of the fentanyl overdose crisis: A case series. *Drug Alcohol Rev*. Published online October 13, 2021:dar.13394. doi:10.1111/dar.13394

Silverstein SM, Daniulaityte R, Martins SS, Miller SC, Carlson RG. "Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl. *International Journal of Drug Policy*. 2019;74:76-83. doi:10.1016/j.drugpo.2019.09.003

Sokolski E, Skogrand E, Goff A, Englander H. Rapid Low-dose Buprenorphine Initiation for Hospitalized Patients With Opioid Use Disorder. *J Addict Med*. 2023;Publish Ahead of Print. doi:10.1097/ADM.0000000000001133

Spadaro A, Faude S, Perrone J, et al. Precipitated opioid withdrawal after buprenorphine administration in patients presenting to the emergency department: A case series. *JACEP Open*. 2023;4(1). doi:10.1002/emp2.12880

Spadaro A, Sarker A, Hogg-Bremer W, et al. Reddit discussions about buprenorphine associated precipitated withdrawal in the era of fentanyl. *Clinical Toxicology*. Published online February 4, 2022:1-8. doi:10.1080/15563650.2022.2032730

Sue KL, Cohen S, Tilley J, Yocheved A. A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era. *Journal of Addiction Medicine*. Published online February 10, 2022. doi:10.1097/ADM.0000000000000952

References (4)

Varshneya NB, Thakrar AP, Hobelmann JG, Dunn KE, Huhn AS. Evidence of Buprenorphine-precipitated Withdrawal in Persons Who Use Fentanyl. *Journal of Addiction Medicine*. 2021;Publish Ahead of Print. doi:10.1097/ADM.0000000000000922

Weimer MB, Guerra M, Morrow G, Adams K. Hospital-based Buprenorphine Micro-dose Initiation. *Journal of Addiction Medicine*. 2021;15(3):255-257. doi:10.1097/ADM.0000000000000745

CME Post-Test Questions

1. While starting buprenorphine, what is the major induction challenge that patients with fentanyl dependence face?
   a) Sedation caused by buprenorphine
   b) Opioid-induced constipation
   c) Reduction in bone-mineral density
   d) Precipitated/protracted opioid withdrawal

CME Post-Test Questions

2. Which of the following best describes the incidence of precipitated or protracted opioid withdrawal for patients with fentanyl dependence using a traditional induction?
    a) Precipitated/protracted opioid withdrawal almost never occur (<1%)
    b) Precipitated/protracted opioid withdrawal occurs for a minority of patients (likely between 1-35%)
    c) Precipitated/protracted opioid withdrawal occurs for nearly every patient (likely >90%)
    d) Precipitated/protracted opioid withdrawal is not real

CME Post-Test Questions

3. Which approach to non-opioid withdrawal adjuvants (eg. clonidine, ondansetron, loperamide, NSAIDs, etc.) is recommended for patients starting buprenorphine?
    a) Always avoid non-opioid withdrawal adjuvants because they can be dangerous for patients starting buprenorphine
    b) Talk to a pharmacist before using any non-opioid withdrawal adjuvants while starting buprenorphine
    c) Strongly consider co-prescribing non-opioid withdrawal adjuvants based on patient-specific characteristics & concerns
    d) Prescribe one medication from each class of non-opioid withdrawal adjuvants for every patient for every buprenorphine initiation.

CME Post-Test Questions

4. During a low-dose initiation with sublingual buprenorphine, what is the most used and recommended starting dose of buprenorphine?
    a) ≤0.5 mg SL (or equivalent in other formulations)
    b) 2 mg SL (or equivalent in other formulations)
    c) 16 mg SL (or equivalent in other formulations)
    d) 24 mg SL (or equivalent in other formulations

CME Post-Test Questions

4. During a low-dose initiation of buprenorphine, how should clinicians and patients approach the use of full-agonist opioids?
    a) Stop full-agonist opioids at least 24 hours before low-dose initiation of buprenorphine
    b) Stop full-agonist opioids at least 8-12 hours before low-dose initiation of buprenorphine
    c) Continue full-agonist opioids during low-dose initiation of buprenorphine
    d) Alternate buprenorphine and full-agonist opioids during low-dose initiation

CME Post-Test Questions

5. What is the recommended approach to treating precipitated withdrawal?
    a) Give more buprenorphine and use non-opioid withdrawal adjuvants
    b) Give high doses of benzodiazepines
    c) Give naloxone
    d) Give methadone

CME Post-Test Questions

6. Some patients, clinicians, and researchers are advocating for faster approaches to titrating methadone for patients with fentanyl dependence. What aspect of fentanyl's pharmacology is cited as the predominant rationale for these new approaches?
    a) Fentanyl takes a longer time to clear in the urine (compared to heroin)
    b) Fentanyl is 25-50x as potent as heroin
    c) Injections per day have increased for patients with fentanyl dependence (compared to heroin)
    d) Fentanyl is a CYP34A inducer and increases metabolism of methadone