Buprenorphine Inductions: Options and Innovations

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ASAM Annual Conference, April 2 2022

Disclosure Information

- Jennifer Hartley, PhD MD FASAM
  - No disclosures
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  - No disclosures
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  - No disclosures

The views expressed in this presentation are solely those of the presenters and do not necessarily reflect the position or policy of UCLA, OHSU, Fora Health, the Department of Veterans Affairs, the United States government, or any other university, or organization

Learning Objectives

- Describe unique challenges of fentanyl to buprenorphine transitions
- Appreciate the importance of preparation for transitions and how to utilize a variety of tools for patient support
- Understand low, medium, and high-dose transition approaches described in the literature
- Learn about a residential withdrawal management-based transition protocol using a combination of low and high dose buprenorphine, and the data supporting this method

Quick note on terminology

- "Transition," "start," "initiation" rather than "induction"[1]

> The previous version of these guidelines used the term induction. While the meaning is the same in this context, the Guideline Committee noted that this language did not align with the terminology used for other medical conditions and can make the process sound more difficult and complex than it is.

- "Low dose" rather than "micro" [2]

ASAM 2020 OUD NPG, Weimer 2022

Setting: Pacific NW

- Portland, Oregon
- Fentanyl became significant part of drug market on East Coast earlier, 2013
- More recently dominating opioid landscape on West Coast, within last 2-3 years depending on specific locale[3]
- Preponderance of pressed pills “oxy blue 30s” also in powder form

Shover, 2020

Patient Experiences

"I didn't believe in addiction before. I thought it was just because people are weak. Now I'm taking the blues and I can't get off of them. I never thought this would happen to me."

"If you are on blues you can never get on bupe. You are screwed."

Provider Experiences

"My patients can't manage a microinduction. I've tried and they end up calling my office every day, sometimes more than once, with questions. It seems like the only good option and it's just too complicated."

"A few of my patients have had really bad experiences with precipitated withdrawal going from fentanyl to Suboxone. I'm not sure I can do this anymore."

Planning to Start Buprenorphine

- Prevent poisoning (overdose)
- Manage anxiety
- Prepare for discomfort
- Provide clear instructions
- Schedule close follow up

Prevent Poisoning (Overdose)

- Especially if continuing full agonist while starting buprenorphine
- Discuss risk
- Prescribe Naloxone
  - Some patients prefer injectable
  - High dose (8 mg/dose) controversial[4]
  - Generic 4 mg nasal coming soon (hopefully)

Hill, 2022

Manage Anxiety

- Previous experiences
  - PTSD
- Setting
- Provider confidence
- Meds

Prepare for Discomfort

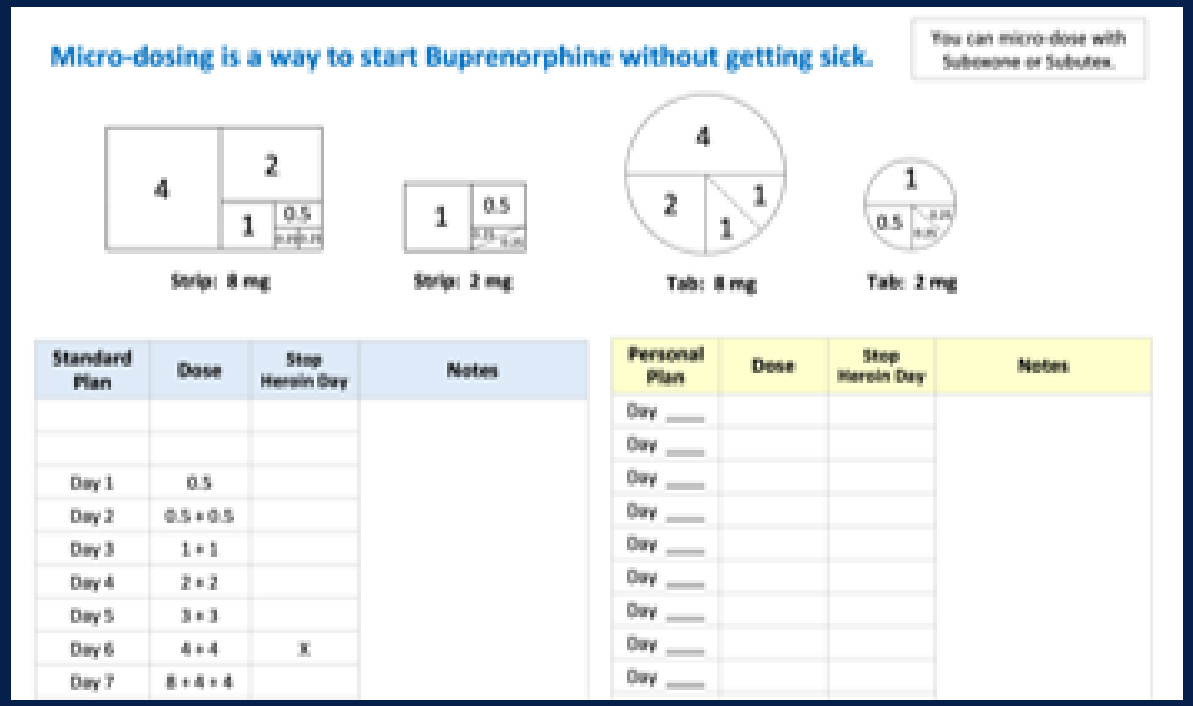
- Profound restlessness and back pain
- Caretaker
  - “Kick buddy” or “Transition doula”
- Baths, massage, back rubs
- Consider scheduled adjuncts

Prepare for Discomfort: Adjunctive Meds

- Acetaminophen and ibuprofen
- Clonidine or Lofexidine[5,6,7]
- Hydroxyzine
- Olanzapine
- Trazodone, Doxepin or Zolpidem
- Tizanidine[5,6] or Methocarbamol
- Gabapentin[8,9,10]
- Ondansetron
- Bismuth or Loperamide
- Benzodiazepines

Srivastara, 2020; Kosten, 2019; Kuszmaul 2020; Kheirabadi 2008 ;Salehi 2011; Sanders 2013

Clear Instructions



Micro-dosing is a way to start Buprenorphine without getting sick.

You can micro-dose with Suboxone or Subutex.

Strip: 8 mg

Strip: 2 mg

Tab: 8 mg

Tab: 2 mg

Standard Plan	Dose	Stop Heroin Day	Notes
Day 1	0.5		
Day 2	0.5 + 0.5		
Day 3	1 + 1		
Day 4	2 + 2		
Day 5	3 + 3		
Day 6	4 + 4	X	
Day 7	8 + 4 + 4		

Personal Plan	Dose	Stop Heroin Day	Notes
Day ___			
Day ___			
Day ___			
Day ___			
Day ___			
Day ___			
Day ___			
Day ___			
Day ___			

- With options if there is flexibility
- Challenging in virtual care
- PDF via email, text
- *Website? App?*

Schedule Close Follow Up

- Use behavioral health staff or peers if you have them
- Planned check in can reduce anxiety
- Have boundaries
- Tell patients you are already prepared with Plan B

Why would we need a Plan B?

- Are fentanyl to bup transitions even an issue?
- What is unique about fentanyl pharmacology?
- What new bup start approaches have been described?
  - Modified standard
  - Low-dose
  - High-dose
  - What about XR Bup?

Are fentanyl - bup transitions even an issue?

- Two small (n=251, n=111), retrospective cohort studies found ***no association between fentanyl use and bup treatment initiation or retention*** compared to heroin use[11, 12]
- An ongoing, multi-site trial of bup starts at 28 EDs shows a 1% risk of precipitated withdrawal in a population with fentanyl present in 76% of UDTs[38]

(Cook 2021, Wakeman 2019, D'Onofrio 2021)

Are fentanyl - bup transitions even an issue?

- However, numerous smaller studies describe ***many unique difficulties managing this transition***

- You came to this talk today!

Some evidence suggests fentanyl withdrawal…

- Starts sooner, lasts longer, is more severe (survey of 114 pts)[13]
- Is more likely to lead to precipitated withdrawal with bup
  - OR 5.2 for precipitated withdrawal with bup (v. methadone) within 24 hrs of fentanyl use (multi-center survey of 1679 pts)[14]
  - Precipitated withdrawal with bup despite extended (24-48 hrs) periods of abstinence and high COWS (4 pt case series)[15]
- Is harder to relieve with bup:
  - "24 mg not uncommonly necessary to manage withdrawal"[16]
  - Only 38% reported bup "completely alleviated" fentanyl withdrawal[14]

Gryczynski 2019, Varshneya 2021, Shearer 2021, Neimark 2020

What is unique about fentanyl's pharmacology?

Fentanyl's **higher lipophilicity and μOR affinity** imparts:[17]

Higher CNS penetration → Higher potency (100 x morphine) → Higher OD risk; Faster development of higher levels of tolerance → **More severe, harder to relieve withdrawal**

Faster distribution → Shorter duration of action → Earlier withdrawal onset

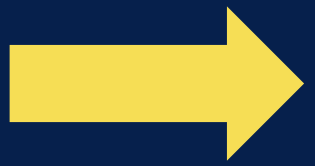
More adipose accumulation → Longer terminal half life (2-7 H) → Longer withdrawal duration

Earlier withdrawal onset; Longer withdrawal duration → **Easier to precipitate withdrawal**

Peng 1999, Huhn 2020, Gryczynski 2021, Neimark 2020, Varshneya 2021, Shearer 2021

The problem in short

More Potent Opioid Supply



Higher Tolerance, More Severe Withdrawal

Same Bup Start Protocol?

What new approaches have been described?

Option 1: modify the standard bup start

	Standard[19]	Modified standard[1,20]
COWS to start	Not specified	≥12-13
Initiation dose	2-4 mg	2 mg
Dosing frequency	~2 hours	1-1.5 hrs
Day 1 TDD	8-12 mg	8-12 mg

SAMHSA TIP 63 2021, ASAM 2020 OUD NPG, Antoine 2022

Low-dose starts: principles[21]

- Gradual displacement of full μOR agonist starting with low (< 2 mg) bup doses
- Full μOR agonist continued until therapeutic bup dose achieved
- Low doses of bup displace some full agonist, but also **resensitize** and **upregulate** μORs, net effect is minimal impact on opioid tone; no precipitated withdrawal
- Bup dosing may be fast (Tpeak ~1 hour), or more gradual
- Ideal in cases where withdrawal of full μOR agonist is especially difficult (e.g. acute pain, methadone, h/o failed traditional bup starts)

An example low-dose bup start protocol			
Day	SL Bup Dose	Total Daily Dose	Full agonist
1	0.5 mg SL once	0.5 mg	Continue
2	0.5 mg SL BID	1 mg	
3	1 mg SL BID	2 mg	
4	2 mg SL BID	4 mg	
5	4 mg SL BID	8 mg	
6	4 mg SL TID	12 mg	Stop
7	8 mg SL BID	16 mg	

Aquino 2021

Low-dose starts: variations[21-25]

- Many approaches described, varying:
  - Speed to therapeutic bup dose (range 1 – 9 days)
  - Formulation/route of bup (SL, transdermal, buccal, IV, SL-by-PO)
  - Use of bridging full μOR agonist (fentanyl patch, SR morphine)
- No prospective comparative effectiveness studies yet published
- Patient selection and preparation (bup-start Hx and preferences, LA-opioid use, current withdrawal state, ability to self-administer doses) likely key to success

	Standard	Low-dose
COWS	Not specified	0
1st dose	2-4 mg	~0.5 mg
Dosing freq.	~2 hrs	1-24 hrs
Day 1 TDD	8-12 mg	0.25 - 12 mg

Aquino 2021, Ghosh 2019, Ahmed 2020, Thakrar 2022, Weimer 2020

High-dose starts: principles

- Defined as day 1 TDD > 12 mg[26]
- Ceiling effect limits risk of AEs[27, 28]
- Bup Cmax ≈ 1 hr[27-29]
- TDDs >12 mg needed for blockade[29] and to fully address withdrawal and cravings, which improves retention in care[30-34]
- Why not get there in 2-3 ***hours*** instead of 2-3 ***days***?

	Standard	**High-dose**
COWS	Not specified	≥ 8
1st dose	2-4 mg	8 mg
Dosing freq.	~2 hrs	1 hr
Day 1 TDD	8-12 mg	16-32 mg

Herring 2021, Walsh 2003, Ahmadi 2018, Greenwald 2015
Danilewitz 2020, McNeil 2014, Simon 2020, Fareed 2012, Jacobs 2015

High-dose starts: the CA-Bridge protocol[26]

- In uncomplicated patients (no: AMS, severe pain/trauma, organ failure, MTD use)
- When ≥ 12 hrs since last SA opioid use AND COWS ≥ 8 AND ≥ 1 objective sign of withdrawal
- Give 8 mg bup SL, in 1 hr, if Sxs improved, give second 8 mg bup SL dose
- May give add'l 4-8 mg q1h prn cravings/withdrawal up to TDD 32 mg

Herring 2021, See also: cabridge.org/tools/on-shift/

High-dose starts: what about adverse events?

- Respiratory depression or sedation: ***0/366 high-dose starts***
- Precipitated withdrawal: ***0/366 high-dose starts***
- Limitations:
  - % fentanyl use not reported
  - Short (median 2.4 hr) Tx episodes
  - Generalizability beyond ER setting (adjuncts, monitoring, med admin frequency)

PS, see "Frontiers in ED Addiction Care" Today 430-530 PM for more from these authors!

Why would this be?

- They *waited* to start bup
- Under-treated withdrawal?
- Precipitated withdrawal?

Either way,

"too little, too soon" means more bup should help

Herring 2021

What about XR Bup?

- Sublocade[35]
  - Small (n=5) study describes high-dose SL → same-day XR-Bup start in office setting with multiple adjuncts (clonidine, clonazepam, zolpidem)
  - Protocol: COWS > 6 → bup SL Q1H: 2 mg, 6 mg, 8 mg, 8 mg → sublocade 300 mg
- CAM2038, "Brixadi" – currently in FDA approval phase
  - Phase 3 protocol:[36] Mild-mod withdrawal → 4 mg bup SL test dose → 16 mg qweek SC dose (equiv to 8 mg bup SL), w/ additional 8 mg qwk doses (equiv to 4 mg bup SL) available on days 4-7 up to max 40 mg qweek (equiv to 28 mg bup SL)
  - NIDA CTN RTC recruiting 2000 participants, ER setting, CAM2038 24 mg (equiv to 16 mg SL bup) vs. standard SL bup start[37]

Mariani 2021, Frost 2019, https://clinicaltrials.gov/ct2/show/NCT04225598

Summary of fentanyl-bup transition approaches

- In many cases high-dose appears fast, simple, and likely to rapidly manage withdrawal, w/o more AE risk
- In other settings (e.g. inpatient with acute pain, outpatient on MTD) low-dose offers great utility
- XR-bup approaches are on the horizon
- More options mean more room for incorporating patient experience, perspectives and preferences to create a tailored plan!

	Standard	Modified	Low-dose	High-dose
COWS	Not specified	≥12-13	0	≥ 8
1st dose	2-4 mg	2 mg	~0.5 mg	8 mg
Dosing freq.	~2 hrs	1-1.5 hrs	1-24 hrs	1 hr
Day 1 TDD	8-12 mg	8-12 mg	0.5-12 mg	16-32 mg

One approach in a Community-Based Residential Withdrawal Management Setting

"Thank you for adapting to the Blues Pandemic"

Our solution: Low Dose + High Dose

Protocol Development Process

- Patient-informed iterative quality improvement:
  - Continuously observed & collected patient & nursing feedback
  - 3 months of small, non-protocolized trials of different bup and adjunct dosing schemes
  - 1 month for lit review, writing, launching new protocol
  - Ongoing PDSA cycles with multiple protocol updates

Results after three months

	Pts (n)	Lorazepam	AMA	ER Transfer
“Goldilocks”	40	4 (10%)	3 (7.5%)	0
Standard	42	6 (14%)	6 (14%)	3 (7%)

What about patients already in withdrawal?

- After this review, we also modified our standard bup start protocol:

	Old	New
COWS	≥10	≥16
1st dose	4 mg	8 - 24 mg
Dosing freq.	2 hr	1 hr
Day 1 TDD	16 mg	32 mg

If severe withdrawal happens

(and it will sometimes!)

- Use more bupe! Up to 32 mg
- FDA labeling *recommends* 12 mg on day one -- *guideline only*
- According to SAMHSA guidelines, more is okay!
- Use a benzodiazepine when needed. A small dose at the right time can make all the difference in patient experience and success
  - *1 mg lorazepam or 5 mg diazepam or 25 mg chlordiazepoxide*
- Use other support modalities: movement, massage, shower, bath, hot water bottle, fan ……
- Reassure – *this will pass*

Anticipatory Guidance
"Set up for success"

- Ask the patient if they have been through this before; what did they do & how did it go?
- What are they most worried about?
- Prepare them for what may happen – be Realistic!
- Reassure, Reassure, Reassure!!
- Identify a support person
- *"We can get you through this!"*

Continued challenges & questions

- Patients using very high amounts of fentanyl (30 Blues and above daily)
- Which protocol is best for which patient?
- How can we better predict who will have difficult withdrawals?

Final Takeaways

- Careful planning can help patients feel more comfortable with a fentanyl to buprenorphine transition and likely increases success of these transitions and general retention in care
- There is no longer a one-size-fits-all approach to starting bup. Low, medium, and high dose protocols should all be considered, with a plan tailored to the care setting, clinical situation, and patient experience & preferences
- We are all figuring this out together. Trust your close clinical observations, keep eyes open for new patterns. Let patients teach you.

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