AETC AIDS Education & Training Center Program Mountain West

“Microdosing” Buprenorphine Inductions (aka Low-Dose Initiation)

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Disclosures

No conflicts of interest or relationships to disclose

OUTLINE

- A refresher on buprenorphine pharmacology
- The trouble with standard induction
  - For patients transitioning from methadone maintenance
  - For patients transitioning from opioids for chronic pain
  - For patients using illicitly-manufactured fentanyl
- The idea behind microdosing inductions
- The evidence behind microdosing inductions
- Sample approach

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Disclaimer

- “Microdosing” is not an FDA-approved use of buprenorphine/naloxone.
- Literature is thus far limited mainly to case reports, case series, and two larger retrospective cohort studies (in-patient), and there are no evidence-based protocols. There are, however, accumulating clinical experience and RCTs in the works.

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Properties of Buprenorphine

Partial agonist at mu receptor

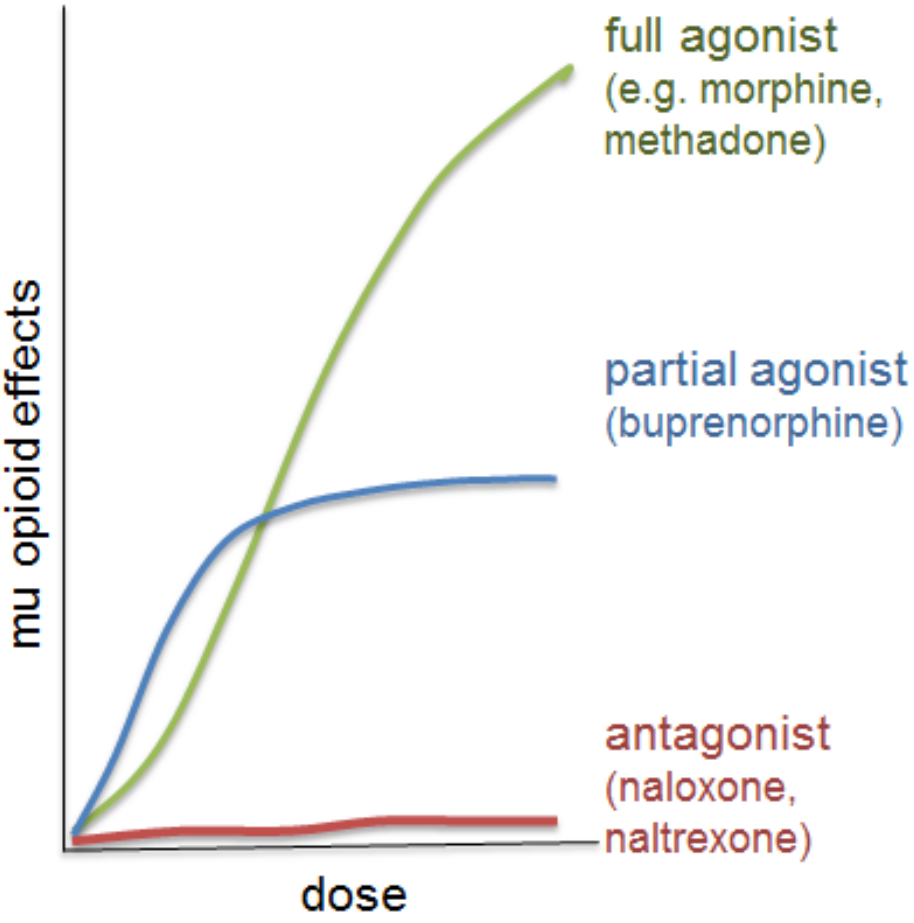
- Comparatively minimal respiratory suppression and no respiratory arrest when used as prescribed

High affinity for mu receptor

- Blocks other opioids

Slow dissociation from mu receptor

- Stays on receptor for a long time ~ 24-36 Hours



Adapted from PCSS Buprenorphine waiver training

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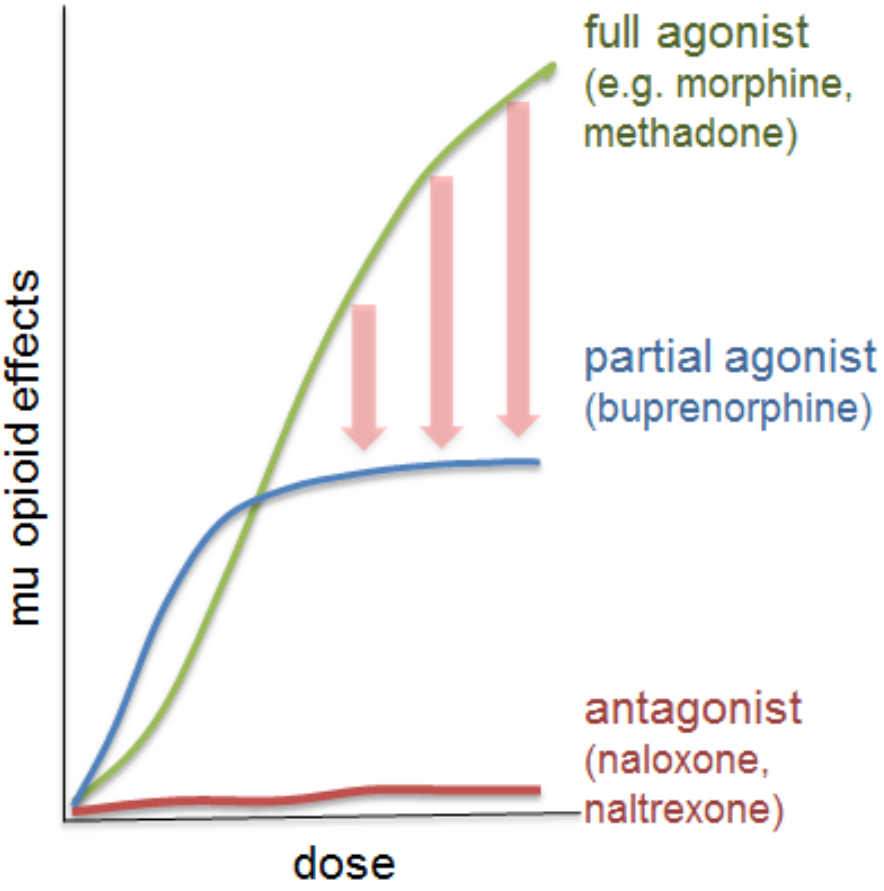
Properties of Buprenorphine

These unique properties make buprenorphine effective at:

- Treating opioid withdrawal
- Minimizing craving
- Blocking reinforcing effects of other opioids
- Not inducing respiratory depression

They also make **initiation** challenging due to the risk of PRECIPATED WITHDRAWAL



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Traditional Buprenorphine Induction

- For short-acting opioids (including heroin), wait >12 hours after last dose, until in moderate withdrawal
- Take 2-4mg SL as first dose. May repeat 2 hours later and up-titrate (generally to 16mg total daily dose)
- Generally works very well with in-office or home induction (aka “self starts”)

Problems with traditional induction

- Patients on methadone
- Patients with acute or chronic pain
- Patients using fentanyl
- Any patient having trouble starting with standard induction

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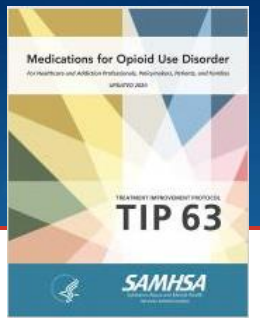
Patients on methadone



- Standard inductions more difficult. Patients generally taper to 30 mg to 40 mg methadone per day and remain on that dose for at least 1 week before starting buprenorphine.
- **Patients tapering from higher doses can face significant risks of return to use during this tapering process.**
- Need to wait 24-48 hours before initiating low doses of buprenorphine.
- “The lower the methadone dose and the longer it’s been since the last dose, the easier the transition.”

Patients with pain

- Patients on chronic opioid therapy may not have as much experience self-managing withdrawal as patients with OUD. The withdrawal necessary in a standard induction may present a substantial barrier to a patient's willingness to rotate to buprenorphine.
- Hospitalized patients with OUD with an acute pain condition may not be able to forgo opioid analgesia long enough for a standard induction.

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Illicitly-manufactured fentanyl

- Though prior pharmacokinetic studies of fentanyl report half lives ranging from 1.5-7 hours, these studies generally relied on brief periods of drug administration.
- Fentanyl is highly lipophilic, allowing it to be sequestered in adipocytes in chronic users, similar to THC.

" I was almost 72 hours into withdrawal --- and I took it [buprenorphine] and it made me . . . I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever . . . But immediately – Bam! Not even five minutes after I took it I was dripping with sweat. It felt like water had just gotten dumped all over me, I'm puking and it's coming out every end."

"[Buprenorphine] sends me into precipitated withdrawals every f**** 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 f**** ask the people that are buying it off the streets. It is real! I waited 80 hours. I was in a detox and after 80 hours they gave me a Suboxone and it still put me into precipitated."

Silverstein et al. Int Journal of Drug Policy, 2019

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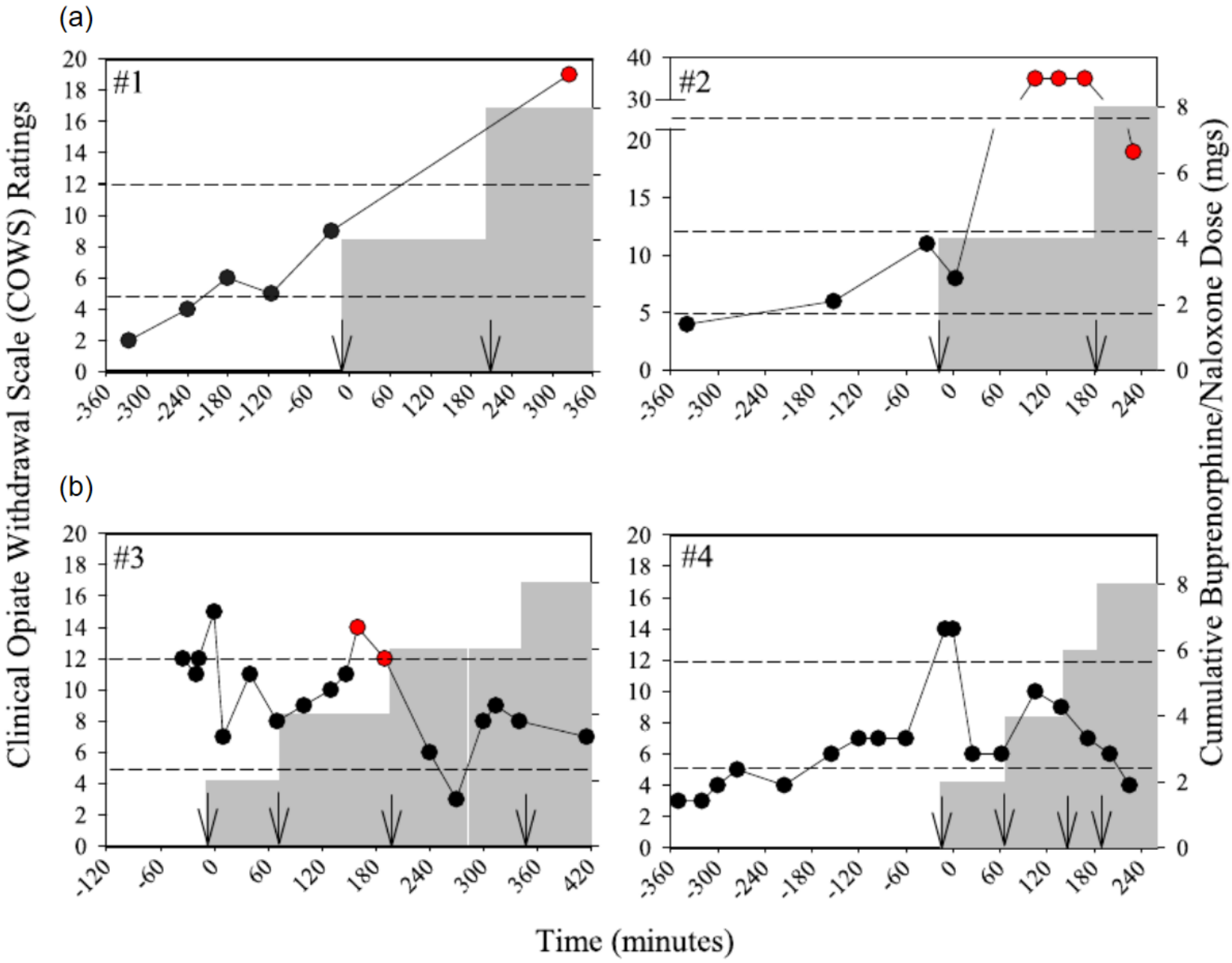

Antoine, D et al. The American Journal on Addictions, 2020

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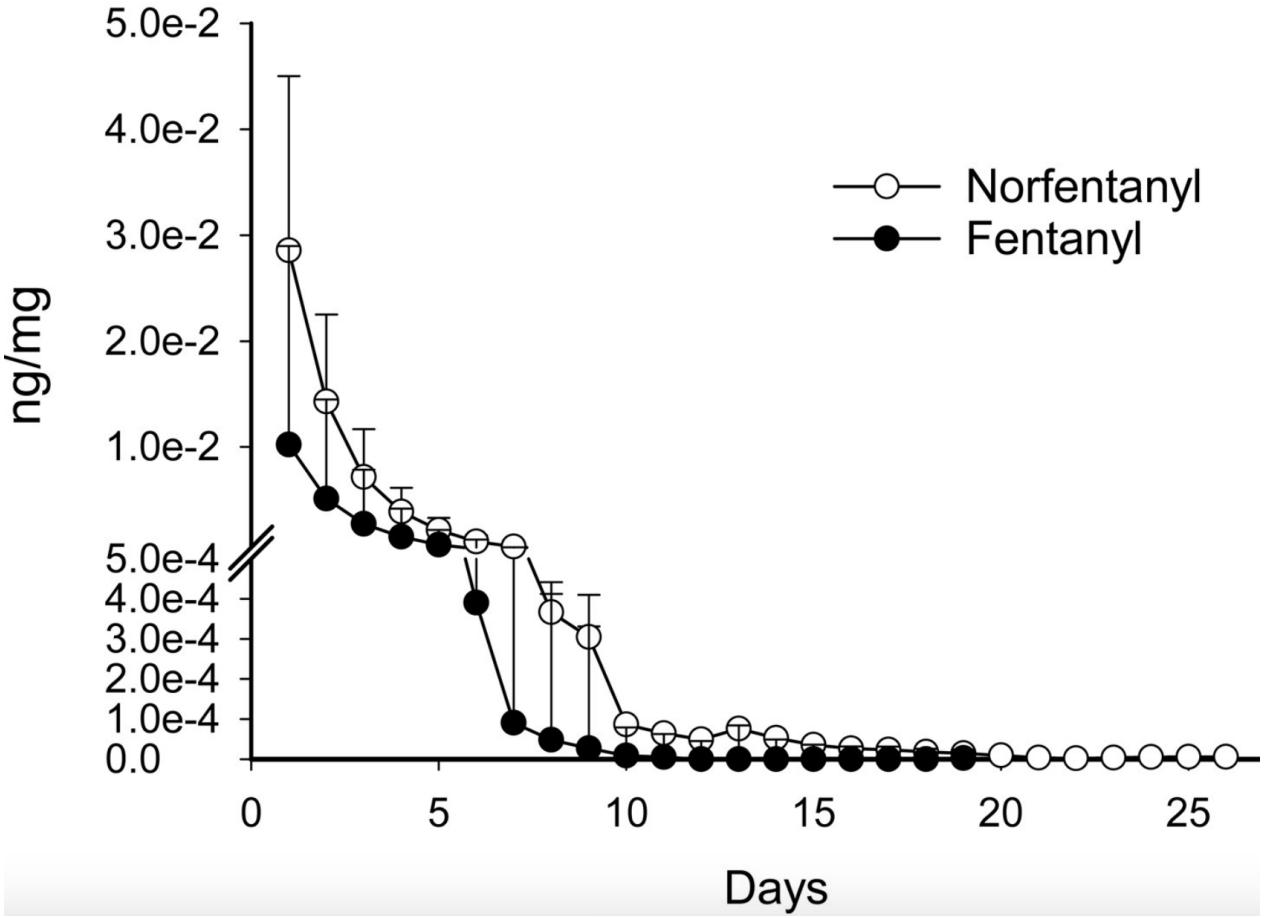
Fentanyl and Norfentanyl Elimination



Mean time for fentanyl clearance: 7.3 days

Mean time for norfentanyl clearance: 13.3 days

Huhn et al, Drug Alcohol Depend, 2020

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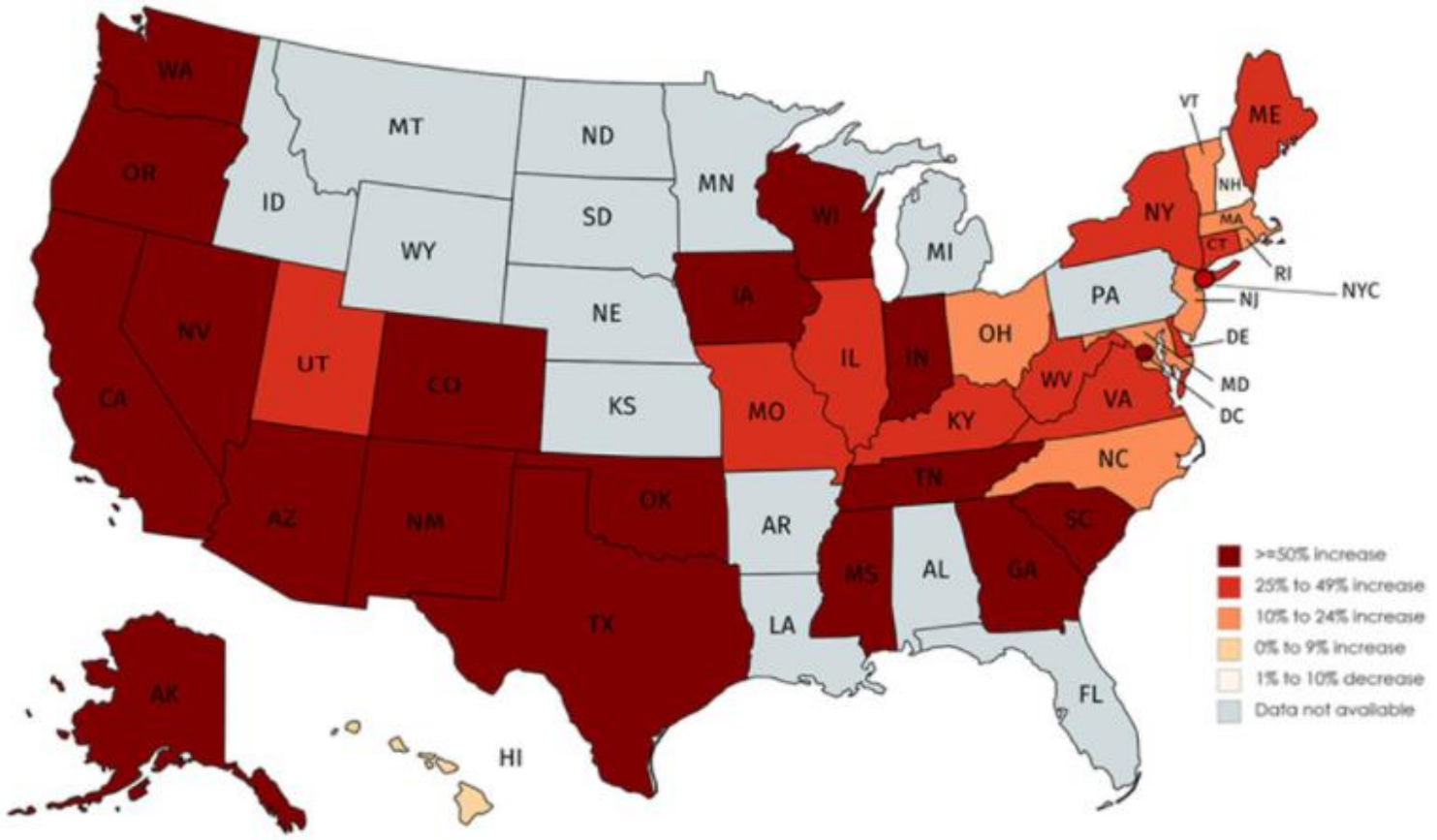
Fentanyl overdoses increasing

Figure 3: Percentage change in 12-months ending provisional[a] count of fatal overdoses involving synthetic opioids[b], 36 states, the District of Columbia, and New York City[c]: Deaths from 12-months ending in June 2019 to 12-months ending in May 2020[d]



HAN Archive - 00438 | Health Alert Network (HAN) (cdc.gov)

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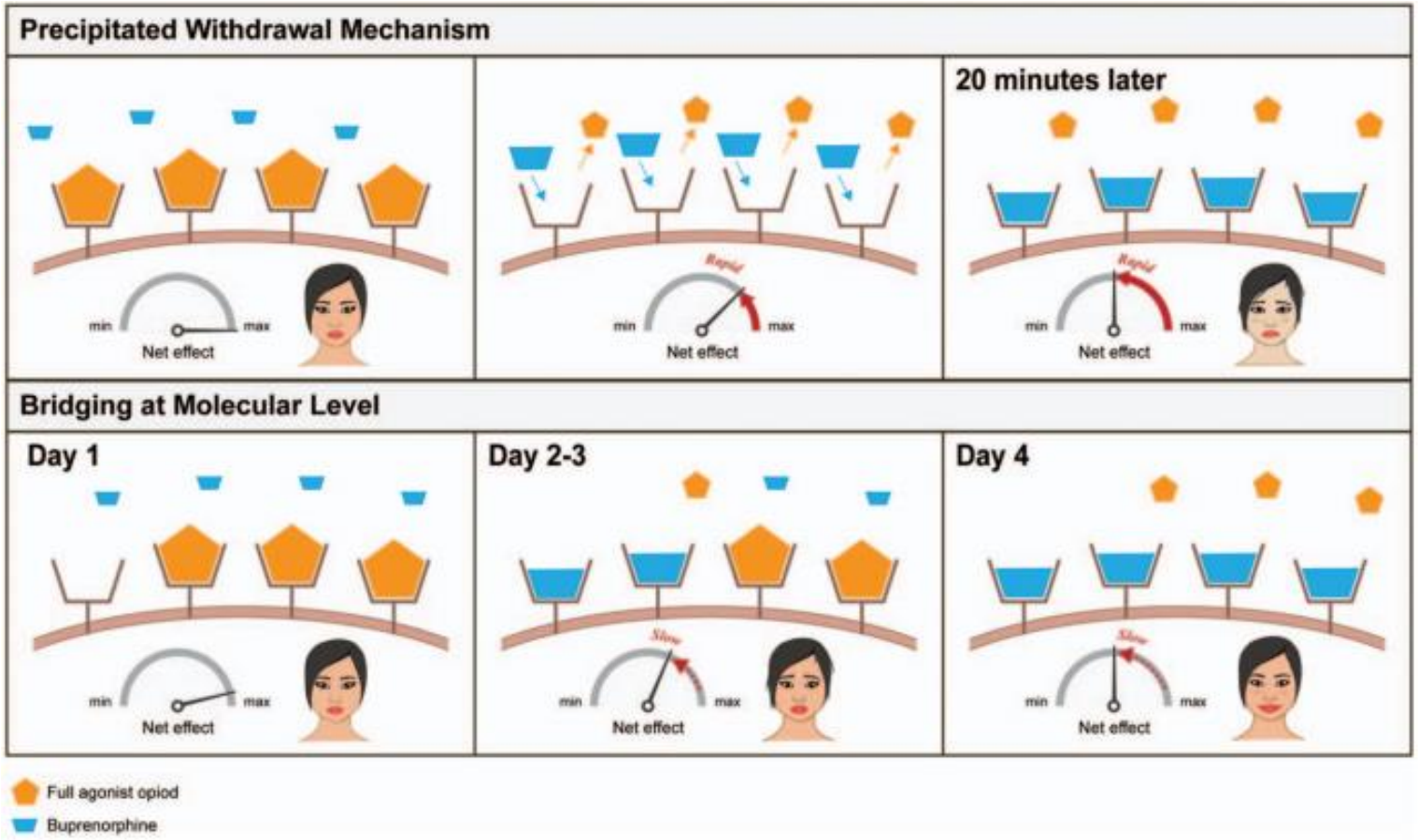
Idea behind “microdosing”

Use ultra low doses to ease buprenorphine onto the receptor while continuing full agonists, to avoid the “wash-out” period of withdrawal



Ghosh et al. The Canadian Journal of Addiction, 2019

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The Bernese Method

Substance Abuse and Rehabilitation
Dovepress
open access to scientific and medical research
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CASE SERIES

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Hämmig et al. *Subst Abuse Rehabilitation. 2016*

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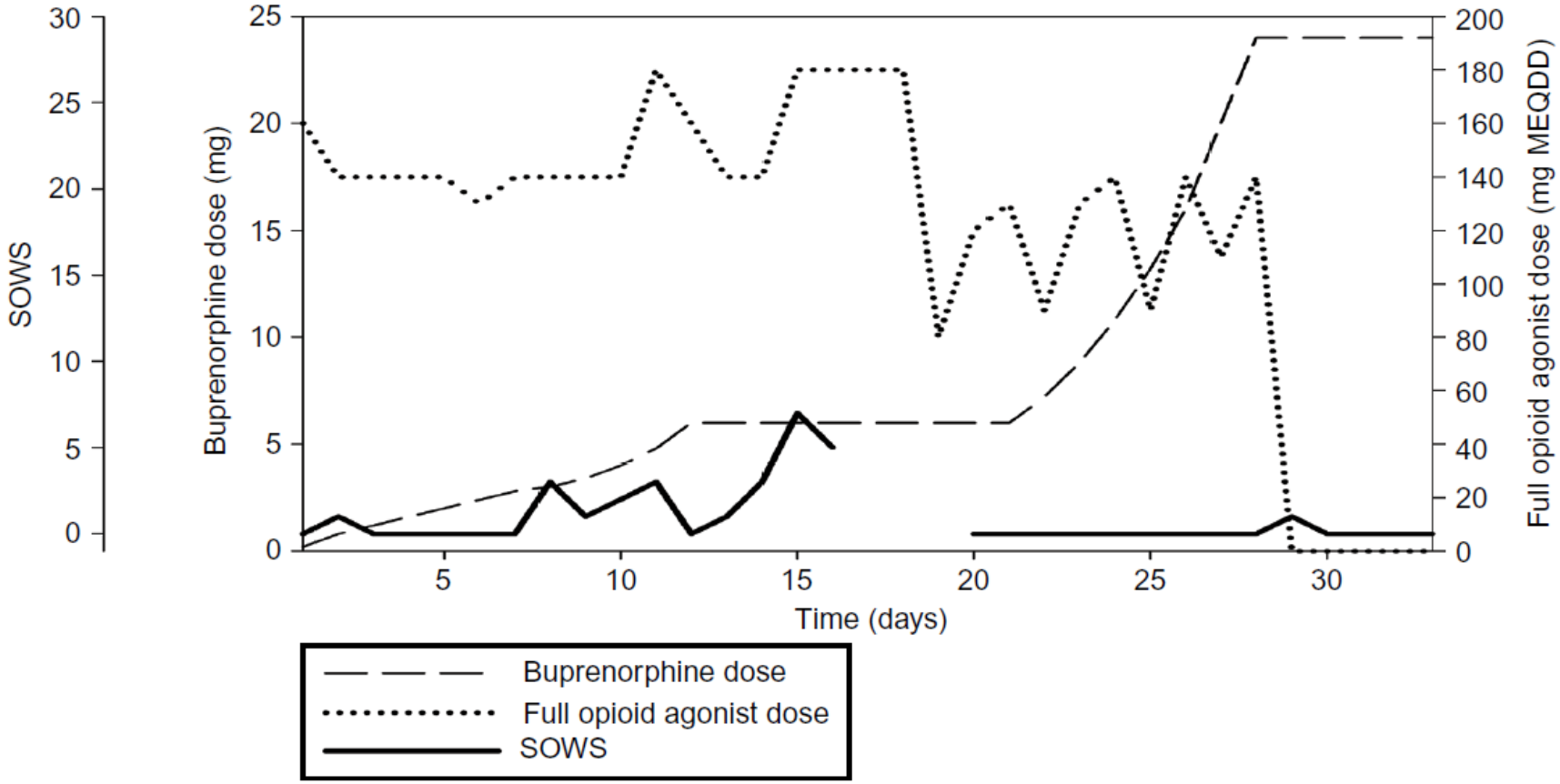

Figure 1 Daily buprenorphine dose (mg), full agonist dose (in MEQDD), and SOWS scores of case 2.
Abbreviations: MEQDD, methadone equivalent daily dose; SOWS, short opioid withdrawal scale.

What's the evidence?

- Systematic Review found case reports and small case series totaling 63 patient experiences in 20 publications
- In ambulatory and hospital settings
- A variety of approaches
  - Transitioned from a variety of opioids over a range of different doses without significant withdrawal
  - Initial doses ranged most frequently from 0.2-0.5mg
  - Various schedules, most over a period of 4-8 days and most completed the cross-titration at 8-16mg of bup

Ahmed et al, American Journal on Addictions, 2020

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OHSU retrospective cohort study

- Mean prescribed MME prior to bup was 198
- Mean duration was 6 days.
- Of the 13 who discontinued
  - 1 transferred to comfort care
  - One attribute SEs to bup
  - 5 had fear of inadequate pain control
  - 2 requested methadone

TABLE 2. Characteristics of Low-dose Buprenorphine Initiations

Induction Characteristic	n (%)
Unique low-dose initiation	72
Reason for low-dose initiation[*]	
Co-occurring pain	66 (91.7)
Anxiety around thought of withdrawal	50 (69.4)
Transition from high dose methadone	21 (29.2)
History of precipitated withdrawal	7 (9.7)
Opioid withdrawal intolerance	5 (6.9)
Other	13 (18.1)
Days of low-dose initiation in hospital – mean (SD)	6 (2.7)
Low-dose initiation completion status	
Completed in hospital	50 (69.4)
Scheduled to complete as outpatient	9 (12.5)
Discontinued in hospital[†]	13 (18.1)
Premature discharge during low-dose initiation	2 (2.8)

[*]Not mutually exclusive.

†One individual did not complete two low-dose initiations before the third, completed low-dose initiation.

Button, et al. J Addict Med. 2021

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HMC retrospective cohort study

TABLE 2. Patient Characteristics and Outcomes

Variable	Successful (n = 51)	Unsuccessful (n = 11)	Total (N = 62)	*P*
Age in years, mean (range)	42 (21–69)	53 (38–67)	44 (21–69)	<0.01
Sex				0.08
M	33 (65%)	4 (36%)	37 (60%)	
F	18 (35%)	7 (64%)	25 (40%)	
Ethnicity				0.45
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Not Hispanic	49 (96%)	10 (91%)	59 (95%)	
Race/Ethnicity*				0.23
White	46 (90%)	8 (73%)	54 (87%)	
Black/African American	3 (6%)	2 (18%)	5 (8%)	
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Asian	0 (0%)	0 (0%)	0 (0%)	
American Indian/Alaska Native	4 (8%)	3 (27%)	7 (11%)	
Other	1 (2%)	0 (0%)	1 (2%)	
Length of stay in days, median (SD), range	28 (24) 4-106	43 (45) 6-156	30 (29) 4-156	0.31
Concurrent non-opioid substance use disorder	41 (80%)	10 (91%)	51 (82%)	0.41
Reason for transition				<0.01
Post-hospital placement	8 (15%)	6 (55%)	14 (23)	
Patient preference/Request	35 (69%)	2 (18%)	37 (60%)	
Patient requests to switch from methadone for OUD to buprenorphine	6 (12%)	1 (9%)	7 (11%)	
Safety concerns*	2 (4%)	2 (18%)	4 (6%)	
Full Agonist at time of switch†				0.59
Methadone started during hospitalization	24 (47%)	4 (36%)	28 (45%)	
Methadone for OUD treatment on admission	9 (18%)	5 (45%)	14 (23%)	
Oxycodone	26 (51%)	3 (27%)	29 (47%)	
Hydromorphone	29 (57%)	4 (36%)	33 (53%)	
Fentanyl	8 (16%)	1 (9%)	9 (15%)	
Other	2 (4%)	0 (0%)	2 (3%)	
Full agonist MED, median (SD), range	217 (239) 12-1065	375 (502) 59–1505	228 (313) 12-1505	0.22
Any withdrawal symptoms reported during transition N (%)	16 (31)	7 (64)	23 (37)	0.03

*Safety concerns included: long QT/arrhythmia (2) prior respiratory arrest on methadone (1) somnolence (1) constipation (1).
†Not mutually exclusive.

Bhatraju et al, 2021

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HMC retrospective cohort study

TABLE 1. Microdose with Overlap Protocol

	Dose of buprenorphine*	Full Agonist
Day 1	0.5 mg once	Baseline dose
Day 2	0.5 mg BID	Baseline dose
Day 3	1 mg BID	Baseline dose
Day 4	2 mg BID	Baseline dose
Day 5	4 mg BID	Baseline dose
Day 6	8 mg Once	Baseline dose
Day 7*	8 mg AM/4 mg PM	Baseline dose
Day 8	8 mg BID	None

*Buprenorphine/naloxone films or tablets were utilized. Buprenorphine specific doses are reported here for simplicity.

- Overall 82% of patients transitioned to buprenorphine.
- 39% of patients endorsed withdrawal symptoms, most were minor and included anxiety, diaphoresis and HA.
- 66% of patients followed up within our healthcare system within 30 days of discharge.

Bhatraju et al, 2021

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Approach to the patient

- These dosing regimens are complicated. Patients must be motivated and organized to accomplish this successfully as an outpatient.
- For patients wishing to transition from methadone, important to have risk/benefit discussion of transition which includes OTP providers. OTP may be able to provide structured transition. More likelihood of success at doses below 80mg.
- Provide plenty of supports (regular visits and/or phone check-ins, can pharmacy provide blister packs, observed dosing through an OTP?).

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Example schedule: 1 week

Example use: Patients with prior failed induction, patients with long-term chronic fentanyl use, patients with withdrawal anxiety/intolerance.

Day	Actual Dose/Day	Fraction of Buprenorphine-Naloxone Film	Opioid
Day 1	0.5mg daily	1/4 film (2/0.5mg) daily	Continue current dose
Day 2	0.5mg BID	1/4 film (2/0.5mg) BID	Continue current dose
Day 3	1mg BID	1/2 film (2/0.5mg) BID	Continue current dose
Day 4	2mg BID	1 film (2/0.5mg) BID	Continue current dose
Day 5	2mg TID	1 film (2/0.5mg) TID	Continue current dose
Day 6	4mg BID	2 films (2/0.5mg) BID	Continue current dose
Day 7	4mg TID	2 films (2/0.5mg) TID	STOP opioid
Ongoing	8mg BID	1 film (8/2mg) BID	

Adapted from Marwah, et al. *Can Fam Physician*, 2020.

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Example schedules: 2 week (e.g. patient transitioning from methadone)

Day	Actual Dose/Day	Fraction of Buprenorphine-Naloxone Film	Methadone Dose
Day 1	0.5mg	0.25 film (2/0.5mg)	Continue current dose
Day 2	0.5mg	0.25 film (2/0.5mg)	Continue current dose
Day 3	1mg	0.5 film (2/0.5mg)	Continue current dose
Day 4	1.5mg	0.75 film (2/0.5mg)	Continue current dose
Day 5	2mg	1 film (2/0.5mg)	Continue current dose
Day 6	3mg	1.5 films (2/0.5mg)	Continue current dose
Day 7	4mg	2 films (2/0.5mg)	Continue current dose
PROVIDER CHECK-IN			
Day 8	5mg	2.5 films (2/0.5mg)	Continue or taper, per patient preference
Day 9	6mg	3 films (2/0.5mg)	
Day 10	7mg	3.5 films (2/0.5mg)	
Day 11	8mg	1 film (8/2mg)	
Day 12	10mg	1.25 films (8/2mg)	
Day 13	12mg	1.5 films (8/2mg)	Stop Methadone
Day 14	16mg	2 films (8/2mg)	

Adapted from Marwah, et al. *Can Fam Physician*, 2020.

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Transdermal patch approach

- For patients rotating for chronic pain, it is possible to use a Buprenorphine patch for the initial doses of buprenorphine. Cost and DEA regulations make this approach more complicated in the outpatient setting.

Button, et al. J Addict Med. 2021

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Troubleshooting

- If one dose is missed during induction, consider repeating the previous day's dose and continue the schedule. If two doses are missed, consider restarting.
- Not generally necessary, but symptomatic management for withdrawal symptom can also be offered (clonidine/tizanidine, loperamide, NSAIDs, hydroxyzine.)

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Take home points

- Buprenorphine initiation without withdrawal “wash-out” period is possible.
- May be a particularly good option for patients who are transitioning from methadone, patients with acute or chronic pain, or patients who have failed prior inductions or chronically use non-prescribed fentanyl.
- There is no evidence-based protocol – plans should be flexible and individualized.
- Dosing regimens can be complicated and patients need to have support to be successful.

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