BUPRENORPHINE/NALOXONE MICRODOSING

UBC CPD RURAL ROUNDS

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OCTOBER 14, 2021

WELCOME & INTROS

DISCLOSURES

- **Dr. Anne Nguyen:**
  - Payments: paid by UBC-CPD for the delivery and preparation of this presentation
  - No other conflicts or disclosures

- **Dr. Erika Kellerhals:**
  - Payments: paid by UBC-CPD for the delivery and preparation of this presentation
  - Advisory board: sat on advisory panels with Indivior, the developer of Suboxone

MITIGATION OF BIAS

- Relationships do not affect my choices in developing content.

SLIDE DECK ACKNOWLEDGMENTS

- Dr. Jason Wale
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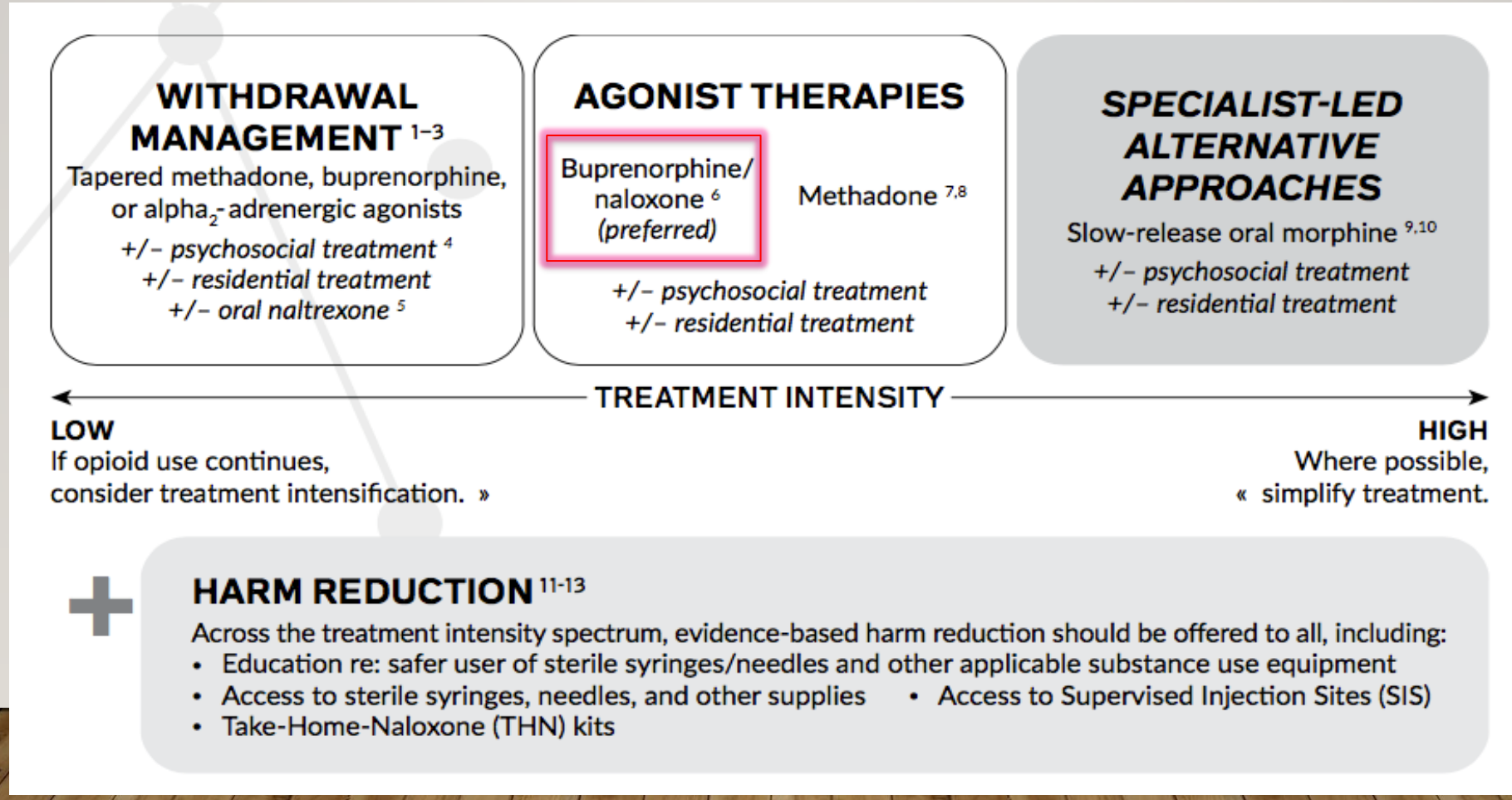
- Dr. Sukhpreet Klaire
- Dr. Theo Jankowski

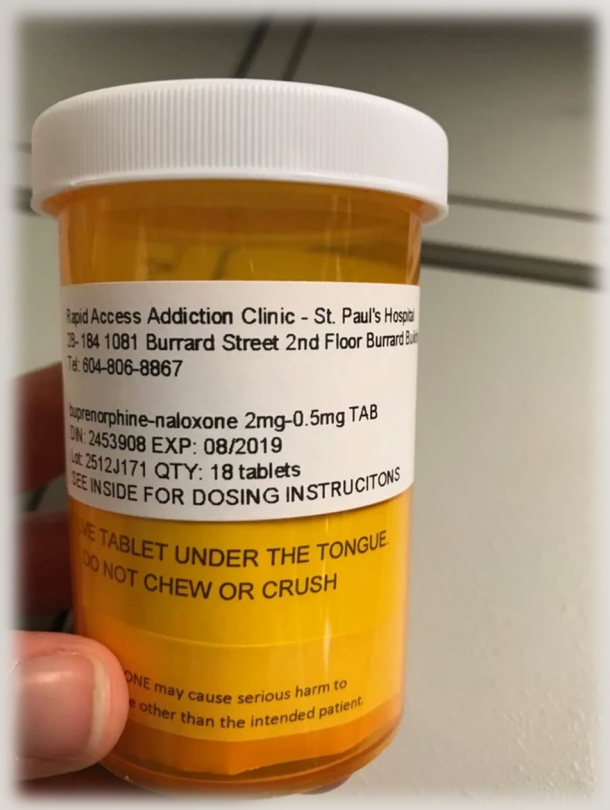
LEARNING OBJECTIVES

- 1. Review Opioid Agonist Therapy (OAT) options and Buprenorphine/Naloxone
- 2. Describe the process of Microdosing
- 3. Describe the rationale of utilizing opioid agonist therapy (OAT) micro-dosing
- 4. Start a patient on OAT micro-dosing in your practice
- 5. Apply this information in a rural community

CONTINUUM OF CARE



"TAKE HOME BUPRENORPHINE"



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JACEP OPEN

WILEY

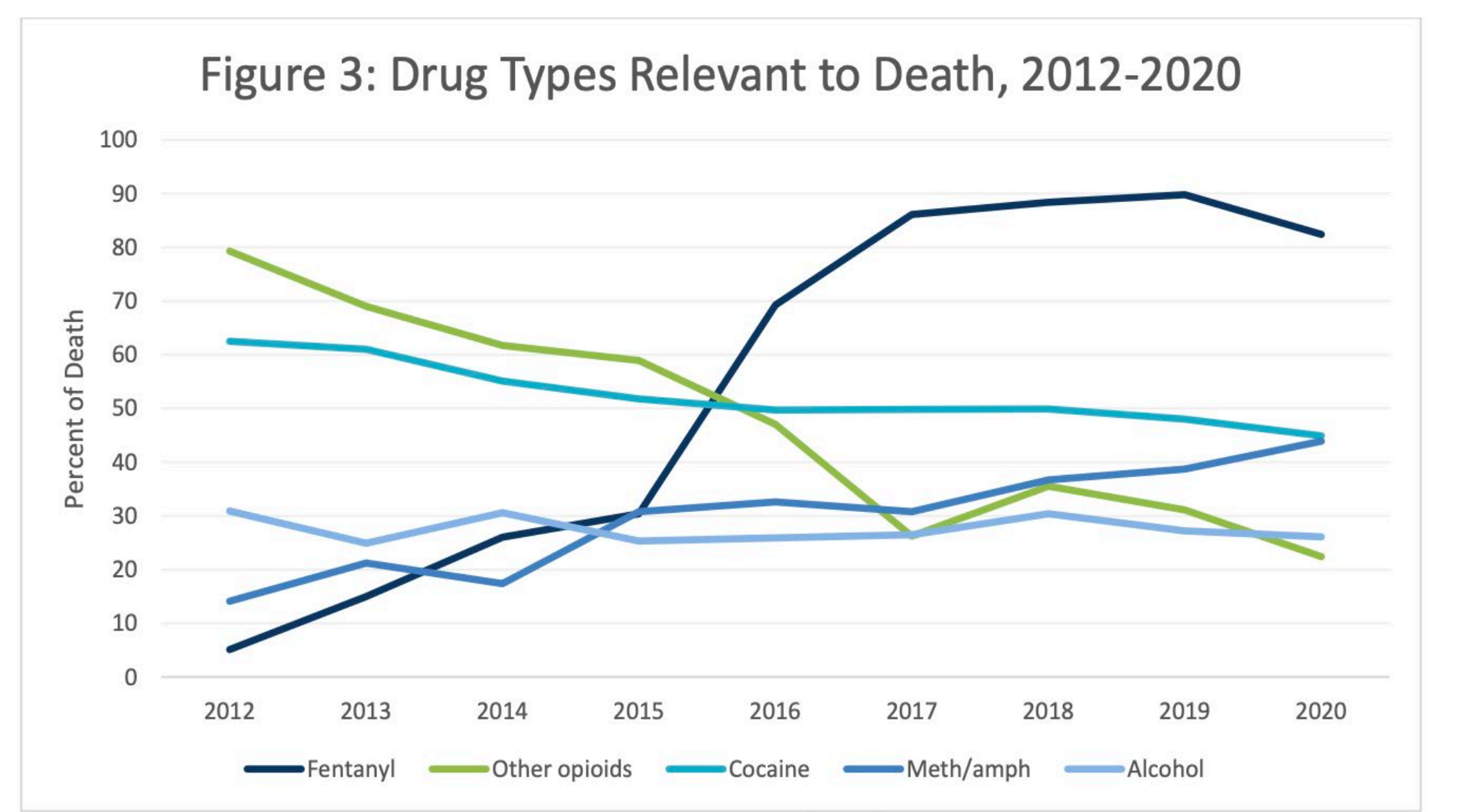
BRIEF RESEARCH REPORT

Toxicology

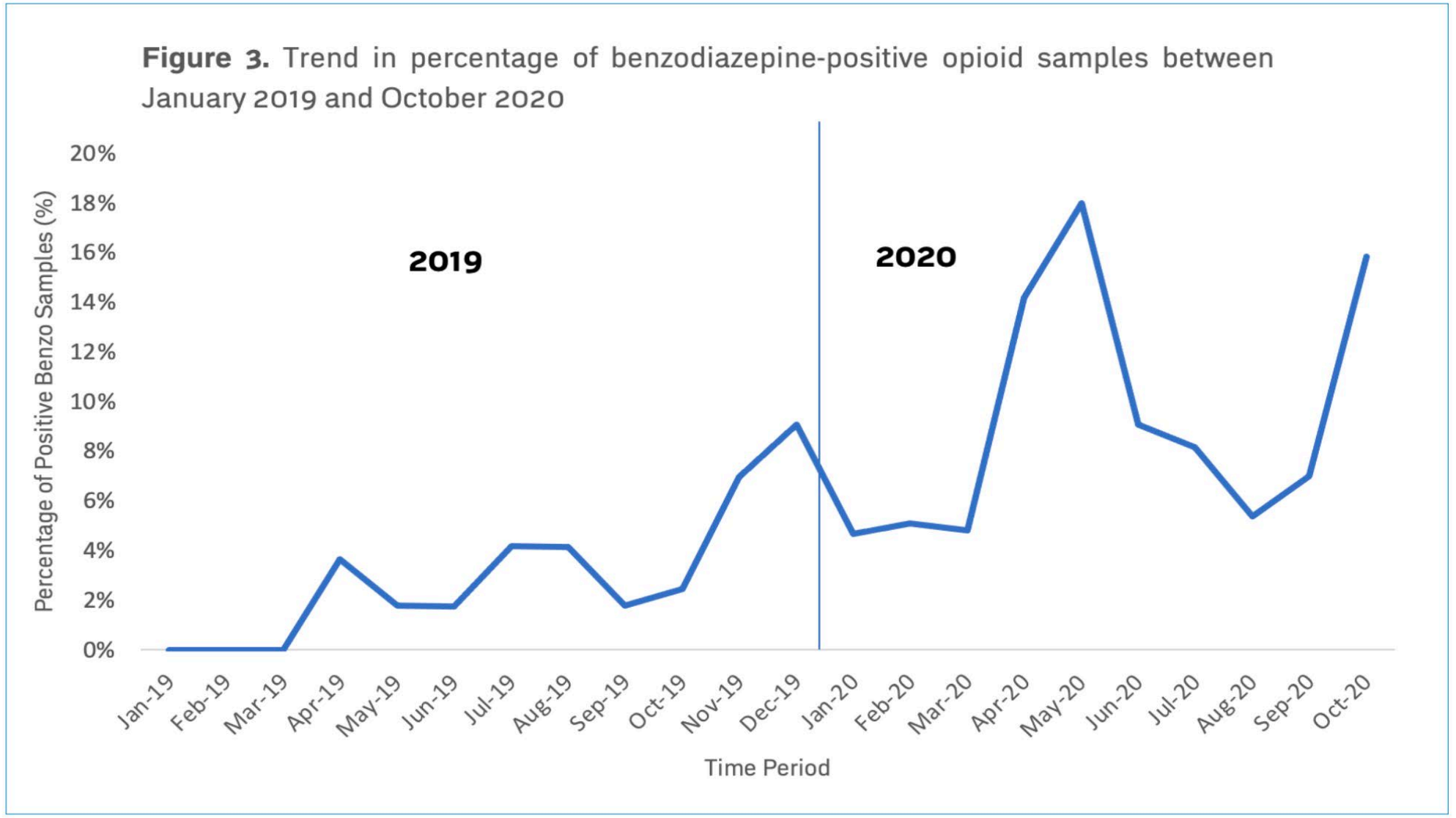
Microdosing and standard-dosing take-home buprenorphine from the emergency department: A feasibility study

Jessica Moe MD, MSc[1,2] | Katherin Badke PharmD, BScPharm[3] | Megan Pratt MSW,

FENTANYL AND METHAMPHETAMINE BECOMING MORE PROMINENT



DANGEROUS ADULTERANTS RISING



BUP/NAL QUICK REVIEW

- Aka buprenorphine/naloxone → 8mg/2mg and 2mg/0.5mg tabs
- Mu opioid receptor partial agonist
  - High affinity → blocks other full agonists (OD protection)
  - Low activity → fewer/less severe side effects, safer w.r.t resp depression
  - Slow dissociation → blocks full agonists, more forgiving if missed doses
  - Duration of action/half-life is dose dependent
    - Typically 32-36h
    - Low dose (<1.2 mg) 3-16 h
- Coverage
  - Covered by pharmacare (Plan G, Plan W) → many patients will need PlanG filled
  - Any doctor/NP can prescribe, no exemption required

INDUCTION OPTIONS

1. Traditional induction in home, office or hospital
    - Stop full agonist for 24-48 hours and ensure moderately severe withdrawal (COWS >/= 12) then start doses of Bup/Nal 2-4 mg every 2-3 hours up to max of 12-16 mg on Day 1
    - Still a great option in the right context
    - Down-sides:
        - Pt needs to undergo withdrawal
        - Treatment destabilization (e.g. they need to “come off” methadone)

2. Microdose → in hospital or at home using telehealth or office appointments for check in
    - New standard of care for most patients
    - Risk of precipitated withdrawal if not done cautiously*

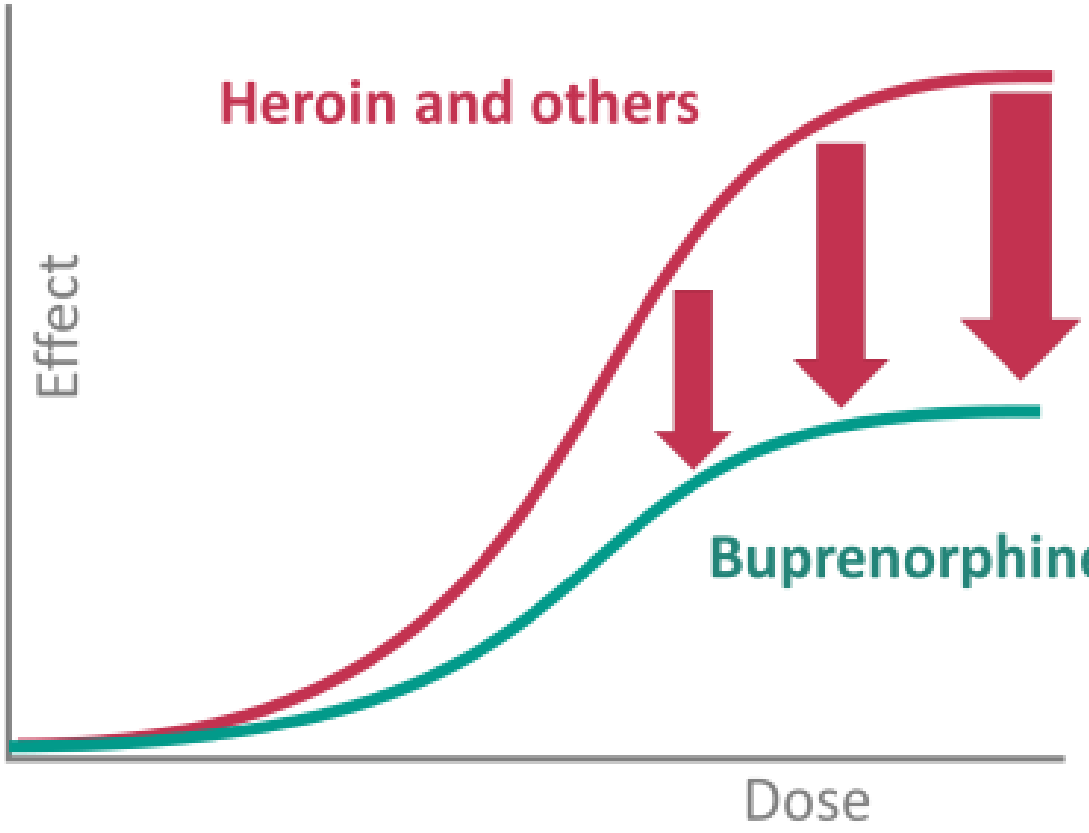
PRECIPITATED WITHDRAWAL → AVOID THIS

Rapid onset of severe withdrawal due to relative reduction in opioid receptor activation by buprenorphine compared to full agonist

Clinically:

- Within ~60 minutes of buprenorphine administration (could be up to 3 hrs)
- May take up to 12hrs to resolve
- Severe withdrawal with rapid onset (precipitous) – sweats, restless, agitated, nausea/vomiting, diarrhea
    - Much more severe than regular withdrawal would have progressed within one hour

Buprenorphine is introduced



Partial activation

- Experienced as withdrawal

Walsh, S. L., & Eissenberg, T. (2003). The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug and alcohol dependence, 70(2), S13-S27.

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CASE SERIES

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

MICRO-DOSING: 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.

WHAT IS MICRO-DOSING?

1. Administer Bup/Nal while the patient remains on their full agonist without waiting for withdrawal symptoms

2. Small doses of bup do not cause clinically significant displacement of other opioids and therefore should not precipitate withdrawal

3. Escalate doses over time to slowly increase receptor occupancy (e.g every 1-24h)

4. Stop full agonist when Bup/Nal is 12 mg OD or higher (unless there's a reason to maintain full agonist)

WHY MICRO-DOSE?

1. You never have to be in severe withdrawal at any point in process → no treatment destabilization and less discomfort
2. Traditional inductions are harder as street supply more fentanylized
   - The high affinity of fentanyl and its analogues in street opioids and their lipophilicity means that people have waited 48 hours after their last use and STILL go into precipitated withdrawal with a properly managed traditional induction
3. Accessible to patients

FENTANYL

ELSEVIER

Drug and Alcohol Dependence

Volume 214, 1 September 2020, 108147

Short communication

Protracted renal clearance of fentanyl in persons with opioid use disorder

Andrew S. Huhn [a, b], J. Gregory Hobelmann [a, b], George A. Oyler [c], Eric C. Strain [a]

Show more

https://doi.org/10.1016/j.drugalcdep.2020.108147

Highlights

- Many persons with opioid use disorder (OUD) are exposed to fentanyl daily.
- Fentanyl clearance was examined in OUD patients in residential treatment.
- Mean fentanyl clearance was 2 weeks, with a range of 4–26 days.
- Protracted fentanyl clearance might affect withdrawal and medications for OUD.

MICRO-DOSING: ADVANTAGES

- Broader availability (compared to methadone, Kadian…in communities without prescribers)
- No treatment de-stabilization
- Minimal withdrawal required

MICRODOSING: DISADVANTAGES

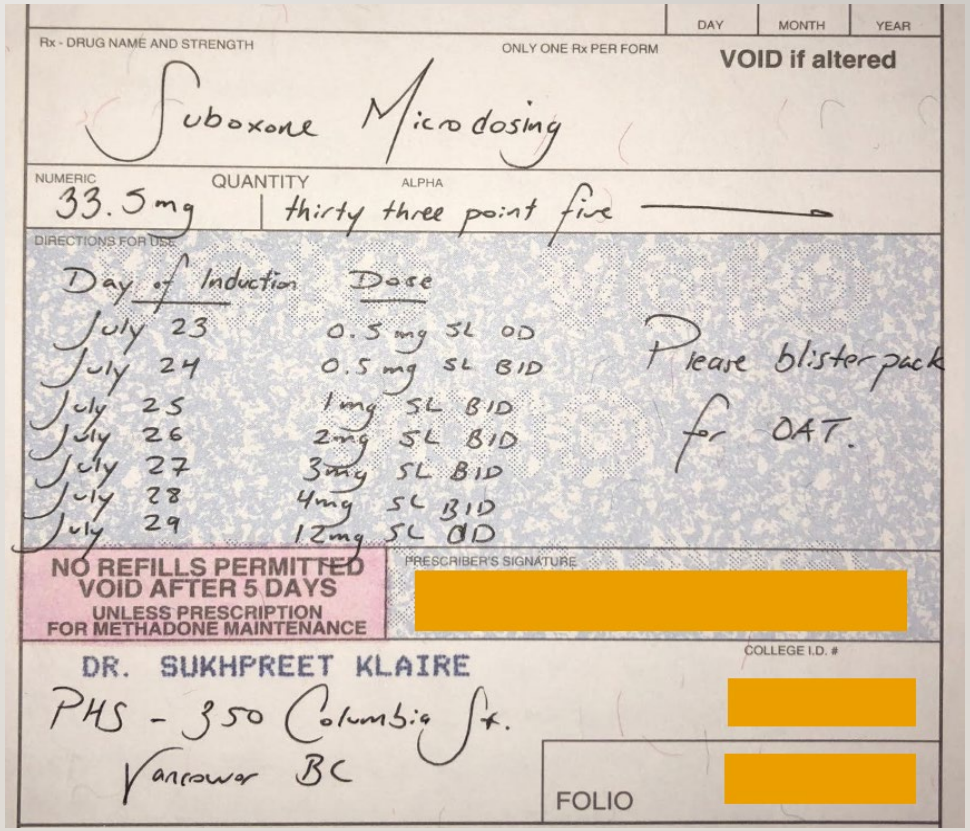
- Longer period of sub-therapeutic doses than traditional induction
- Unclear risk of precipitated withdrawal
  - Especially with Methadone
  - Works best when full agonists are available in the induction phase
- Microdosing works best in hospitalized setting and is more fraught (needs more hand-holding and education) in outpatient setting

HOW TO MICRO-DOSE: TYPICAL OUTPATIENT REGIMEN (FAIRLY QUICK)

- **Day 1**: 0.5mg (quarter of a 2mg tab) twice a day
- **Day 2**: 1mg (half tab) twice a day
- **Day 3**: 2mg (1 tab) twice a day
- **Day 4**: 3mg (1.5 tabs) twice a day
- **Day 5**: 4mg (two tabs) twice a day
- **Day 6**: 12mg in the AM
- **Day 7**: 16mg daily (increase as needed up to 24mg/day)

COMMUNITY PHARMACY MODEL

- OAT dispensed through community pharmacies
- Majority of prescribers use both buprenorphine and methadone or Kadian
- Methadone or Kadian generally DWI, carried doses of buprenorphine very common early in clinical stability



DAY | MONTH | YEAR

Rx - DRUG NAME AND STRENGTH

ONLY ONE Rx PER FORM

VOID if altered

Suboxone Microdosing

NUMERIC: 33.5 mg

QUANTITY

ALPHA: thirty three point five

DIRECTIONS FOR USE:

Day of Induction	Dose
July 23	0.5 mg SL OD
July 24	0.5 mg SL BID
July 25	1 mg SL BID
July 26	2 mg SL BID
July 27	3 mg SL BID
July 28	4 mg SL BID
July 29	12 mg SL OD

Please blisterpack for OAT.

NO REFILLS PERMITTED
VOID AFTER 5 DAYS
UNLESS PRESCRIPTION FOR METHADONE MAINTENANCE

PRESCRIBER'S SIGNATURE

DR. SUKHPREET KLAIRE

PHS - 350 Columbia St.
Vancouver BC

COLLEGE I.D. #

FOLIO

VANCOUVER COASTAL HEALTH PROTOCOL: PRO – OD DOSING…CON -- SLOW

- IF YOU MISS A SINGLE DOSE, WE WILL KEEP GOING, BUT IF YOU MISS TWO OR MORE, WE'LL HAVE TO START OVERSAMPLE SCHEDULE:

DOSE 1	*DOSE 2*	*DOSE 3*	*DOSE 4*	*DOSE 5*	*DOSE 6*	*DOSE 7*	*DOSE 8*	*DOSE 9*	*DOSE 10*
¼ TAB	¼ TAB	½ TAB	¾ TAB	1 TAB	1 ¼ TAB	1 ½ TAB	2 TAB	2 ½ TAB	3 TAB
0.5MG	0.5MG	1 MG	1.5MG	2MG	2.5MG	3MG	4MG	5MG	6MG

A FEW CAVEATS

1. Dispense the whole blister pack
2. Also consider offering DWI full agonist during induction period to take edge off, e.g. Methadone 30-40 mg OD or Kadian 200-400 mg po od
3. Probably best to start early in the week, not Friday
4. Patient education is crucial
   - Give them a sense of control about rate of microdosing
   - The most common time to get precipitated withdrawal is the first 0.5-4 mg
   - What can they do when this happens?
     - Rx a few days of…Seroquel, Clonidine, Ibuprofen, Gravol…depends on what their withdrawal syndrome looks like
     - Call you for guidance; in some patients a small amount of IR Dilaudid might be useful

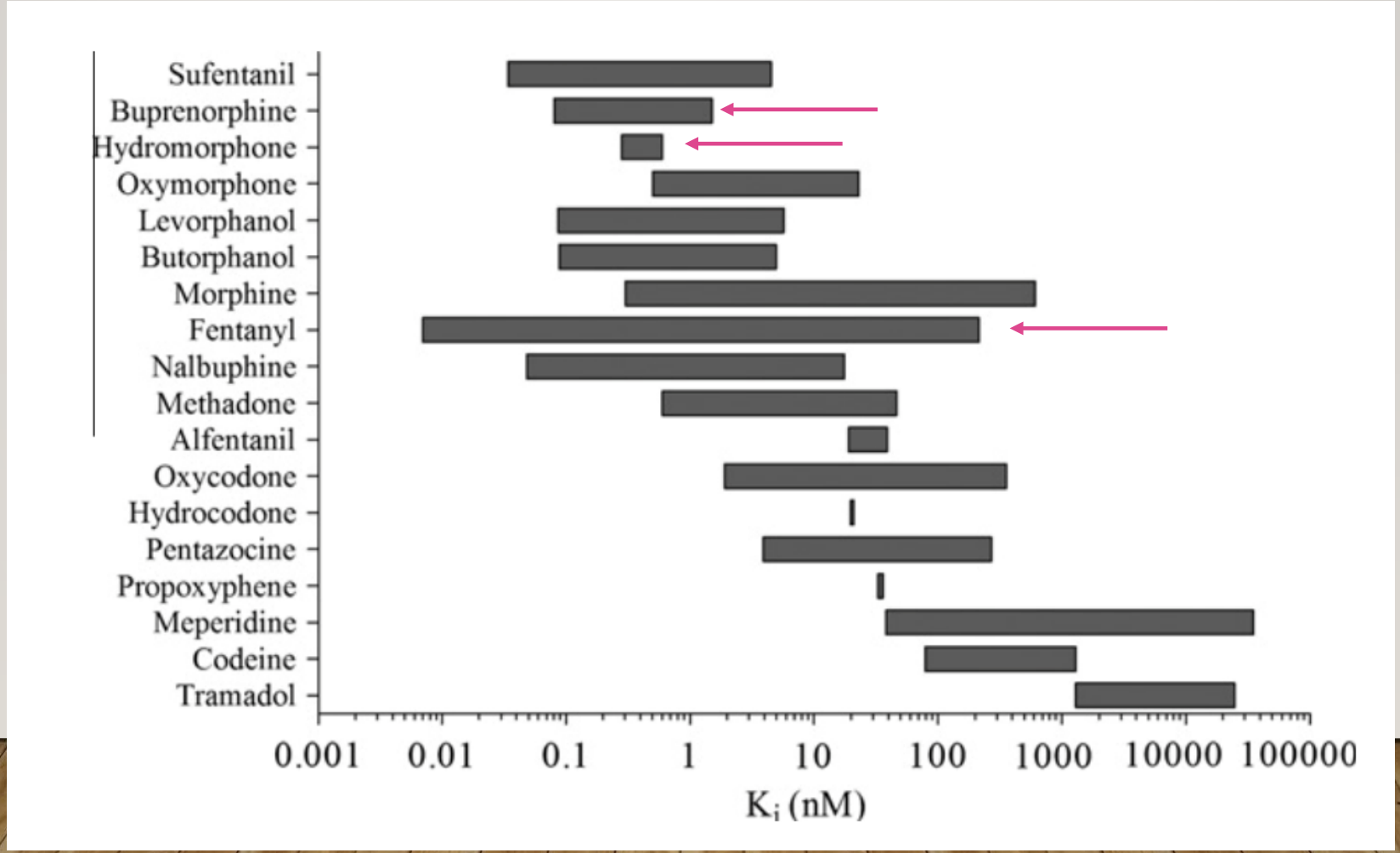
RAPID MICRO-DOSING (IDEAL FOR HOSPITALIZED PATIENTS)

- **Day 1**
  - Continue full opioid agonists
  - Bup/Nal 0.5 mg SL q 3h x 8 doses scheduled (wake up patient overnight)
  - Hydromorphone 3-6 mg po or 1.5-3 mg IV q 3h PRN for any withdrawal
- **Day 2**
  - Continue full agonists
  - Bup/Nal 1 mg SL q3h x 8 doses scheduled
  - Hydromorphone 3-6 mg po or 1.5-3 mg IV q 3h PRN for any withdrawal
- **Day 3**
  - Stop full agonists (including HM)
  - Bup/Nal 12 mg SL scheduled plus Bup/Nal 2-4 mg q 2h prn for up to max of 24-32 mg Bup/Nal total

PRECIPITATED WITHDRAWAL & MICRODOSE TROUBLESHOOTING

- Shouldn't happen with microdose induction, but…
- However, if patient does develop mild withdrawal symptoms, options for management are:
  - Slow down rate of induction (e.g. hold upcoming dose)
  - Use higher frequency and lower doses of Bup/Nal, e.g. doses of 0.5 mg q 3h rather than 1 mg BID
  - Use symptom management meds (analgesics, anti-emetics, anxiolytics)
  - Give a full agonist that is as competitive as Buprenorphine to address withdrawal symptoms, i.e. Dilaudid
  - Stop Bup/Nal induction and opt for one of the other first line OAT options → usually methadone or Kadian
  - In a rural setting, you could hospitalize the patient for 2-3 days to do a rapid microdose induction with PRN dilaudid

BINDING AFFINITY



BUP/NAL MAINTENANCE

- Titration
  - Titrate to at least 12-16 mg (for maximal occupancy of opioid receptors)
  - Max dose: 24-32 mg
  - BID dosing can be useful for patients with chronic pain
- Carries
  - Eligible immediately for carries, e.g. WI once weekly, blister pack 6/7 is very typical starting regimen but that's up to your clinical judgement
  - Balancing risk of diversion vs. risk of patient not taking medication if it's too high barrier
- UDS
  - Per BCCSU guidelines, 4-8x/year would be great

CASES

CASE: 1

- 25 year old man who is unhoused in Campbell River.
- You are seeing in ER post overdose. Know to have severe polysubstance use disorder (fentanyl + crystal meth).
- He is voicing a desire to be on Bup/Nal.
- PharmaNet shows recently off Olanzapine (was on for query bi-polar? Stimulant induced psychosis).
- He is drowsy but rouses to voice.
- Pupils 3mm, HR 70. Orientated x 3.

WHAT'S NEXT? SHARE YOUR IDEAS IN THE CHATBOX.

PEARLS

A) Further Hx:

- Using on average 5-10 pt fent/day
- 3 Previous OD this year
- Hep C Genotype #1 untreated
- PharmaNet shows short trials Methadone + Kadian past year

B) Px:

- COWS (Clinical Opiate Withdrawal Scale) score low 4:
  - Pupils – 1
  - GI Upset – 1
  - Anxious – 1
  - Tremor – 1
- Needle tracks arms + jugular

PEARLS

C) Labs:

- Negative - CBC, RF, LFT, lytes previous GCMS shows etizolam contamination

D) Plan: +++ Markers vulnerability

- Admit:
  - Scheduled + prn SA opioid (HMO)
  - Scheduled kadian 200-300mg
  - Bup-Naloxone rapid microdose
- Discharge:
  - 4 days later on Bup-Nal 24 mg (think about Bul-Nal XR)
  - Has seen psych/ POS Wellness Nurses
  - Harm reduction
  - ST F/U
  - MHSU linkages
  - D/C what to do if relapse

CASE: 2

- 50 year old man transported to your hospital → Port McNeil.
- 2/52 rollover Motor Vehicle Accident on the Malahat + had sustained: bilateral calcaneal #'s, # R scapulae, C5 vert body compression, skull fracture + ruptured spleen
- At time of accident, UDS positive: cocaine, HMO, oxycodone + morphine.
- Pt returns to you on HMO 4-8mg q4 +hr po + HMO 2-4mg q2 hr prn
- Average day seems to use 60-70mg HMO/daily
- Pre accident many chronic pain issues: OA knees, OA hands + DDD lumbar spine.
- Pt was known to seek frequent Tylenol #3 + Tramadol scripts

WHAT'S NEXT? SHARE YOUR IDEAS IN THE CHATBOX.

PEARLS

A) Ascertain if Pt has substance use disorder. In this case, Pt meets 4/11 criteria for opioid use disorder

B) Discuss options with Pt. Bup-Nal increased use for chronic pain but still off label. Talk about Bup-Nal safety profile carries, etc. Classic versus traditional induction

PEARLS

C) Talk about adjusting to Bup-Nal

D) This fellow could do microdose induction most easily but traditional induction still an option

PEER SUPPORTED ED BASED BUP/NAL MICRODOSE PROJECT

- Starting May 2021 in CR (already started in Victoria)
- Bup/Nal Microdose to-go “starter packs” are now available from emergency departments (ED) in CR, CVH and VGH/RJH
- Starter pack contains Bup/Nal 0.5mg x 6 doses. Patient to take one dose twice a day for three days.
- This is meant to be only the start of a full induction. It is incomplete. Needs to be continued by community OAT clinic.

CONTINUED

- Patients with OUD who are open to getting connected to therapy can start this when they leave the ED.
  - Provided local follow up OAT clinic and resource information.
  - Urged to follow-up immediately to continue Bup/Nal induction.

- Patients are encouraged to provide consent to having a referral made to CR peer.
  - The peer will reach in the next day or so to provide encouragement and assistance in contacting an OAT clinic.

RESOURCES

- **RACE** (Rapid Access to Consultative Expertise) - Provincial Race Line for addiction medicine
  - **Phone Number:** 1-877-696-2131
  - **Hours:** Monday to Friday from 0800-1700

- **24/7 Addiction Med Line** (run by BCCSU)
  - **Phone Number:** 778-945-7619

- **BCCSU Clinical Care Guidance Page**: https://www.bccsu.ca/clinical-care-guidance/

- Inpatient Related Issues: folks can call their nearest AMCS

- For specific questions, feel free to contact Dr. Erika Kellerhals at **phone:** 250-287-0536 or **email:** erika.kellerhals@outlook.com