BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

*Networking researchers, educators & care providers*

# OAT Transitions - focus on microdosing

Mark McLean MD MSc FRCPC CISAM DABAM

# Disclosures

- No pharmaceutical industry or other financial conflicts of interest
- Study Physician for research funded by Canadian Institute of Health Research
- Work with:
    - St Paul's Hospital - Rapid Access Addiction Clinic – Medical Lead
    - St Paul's Hospital – Addiction Medicine Consult Team
    - VCH – Vancouver Detox – Medical Lead
    - St Paul's Goldcorp Addiction Medicine Fellowship Program

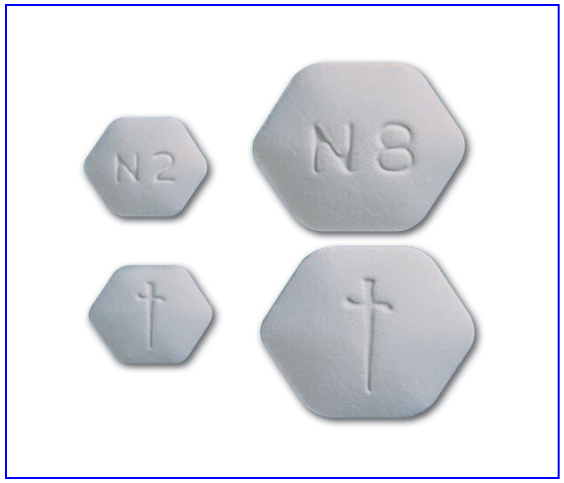
# Buprenorphine Mechanism of Action

- Mu – partial agonist, with high affinity
- Kappa – antagonist
  - Delta – antagonist
  - ORL - agonist

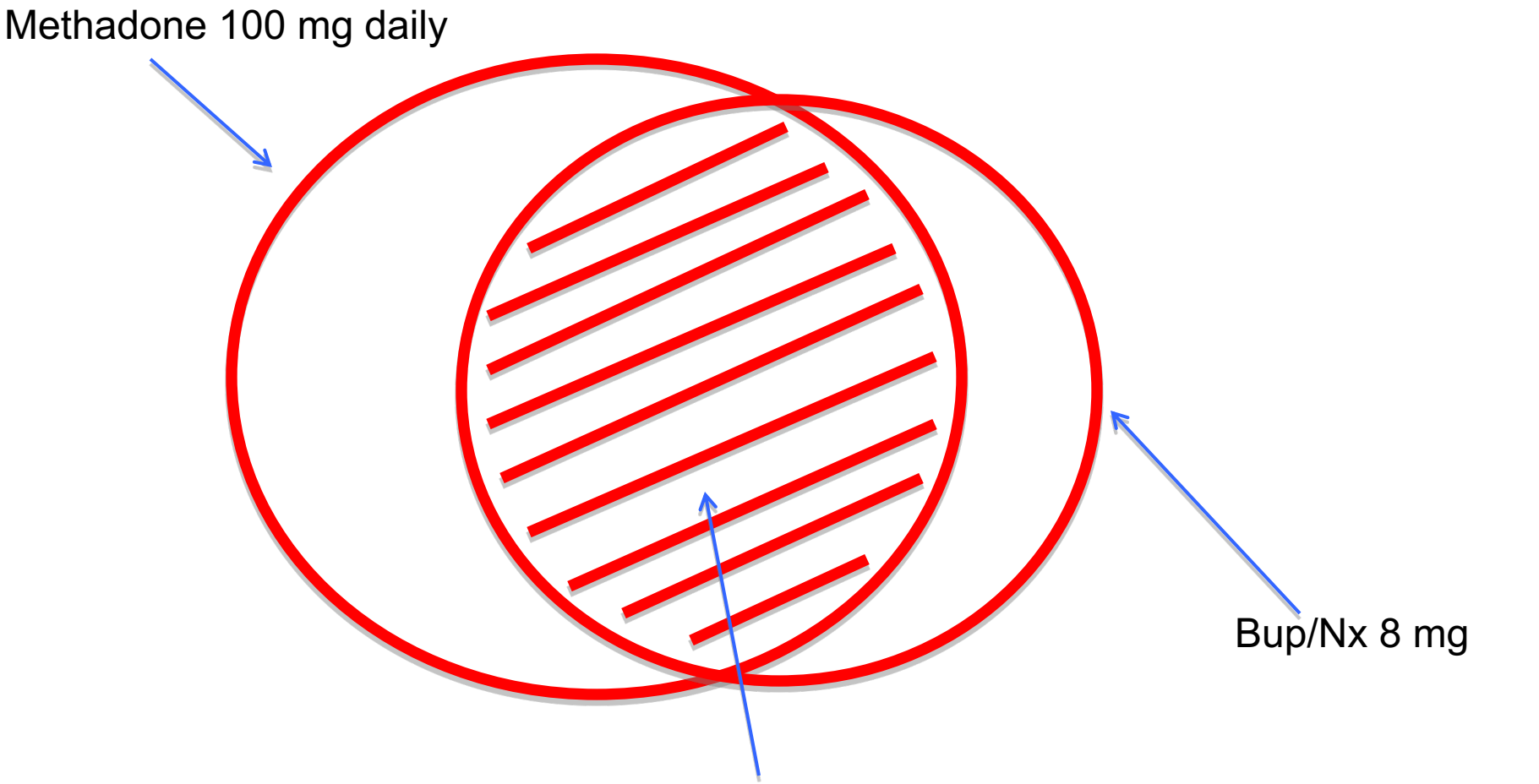
Pedro Ruiz; Eric C. Strain (2011). Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook. Lippincott Williams & Wilkins. p. 439. ISBN 978-1-60547-277-5.

# Buprenorphine/naloxone

- Sublingual tablet
- Fixed combination of buprenorphine and naloxone in a 4:1 ratio
- 2 strengths:
  - Buprenorphine 2 mg/naloxone 0.5 mg
  - Buprenorphine 8 mg/naloxone 2 mg
- Efficacy and safety equivalent to buprenorphine with lower potential for misuse




# What Happens in Precipitated Withdrawal



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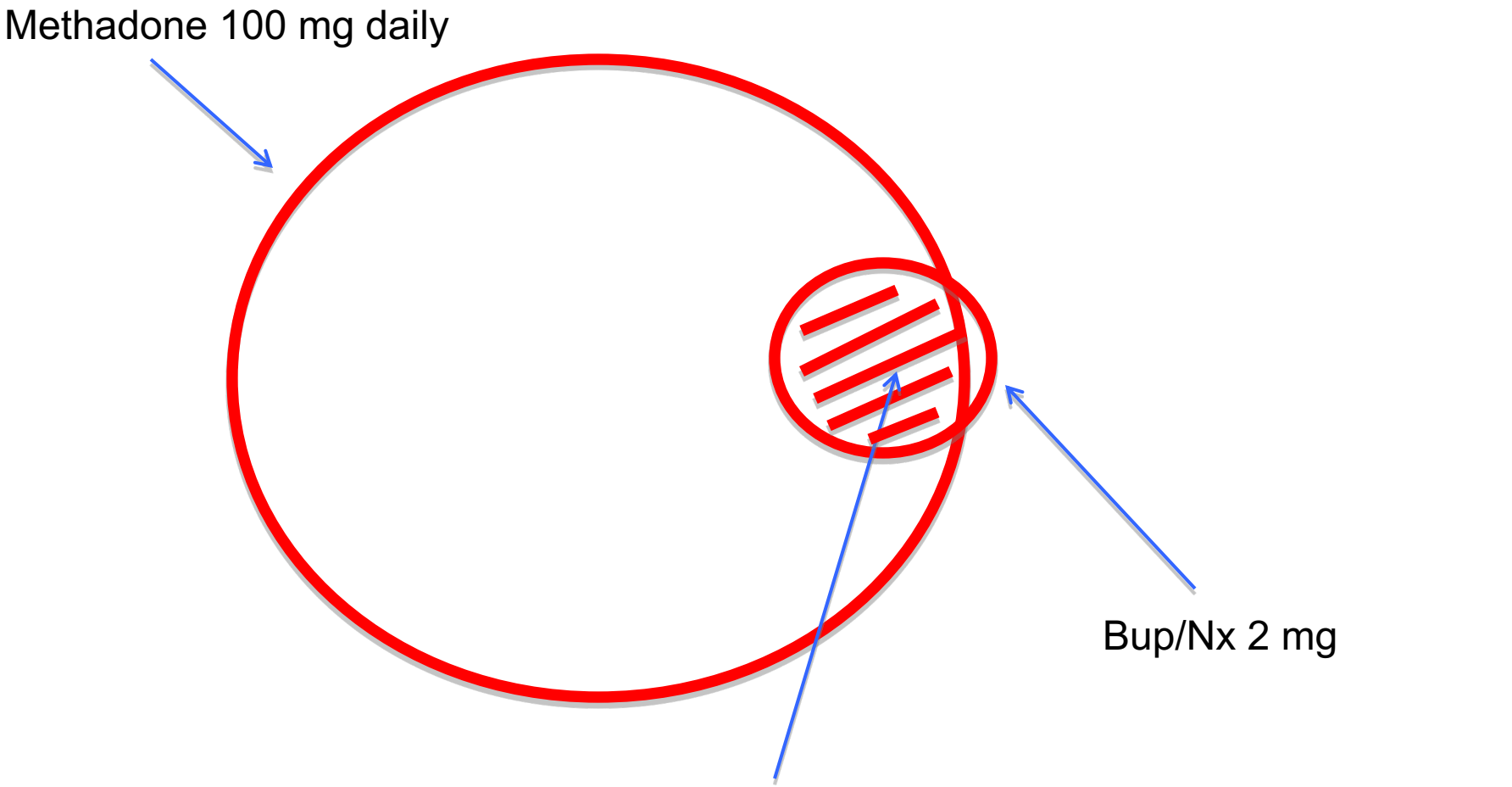


Full agonist displaced by partial agonist ➔ Precipitated withdrawal

# Mu receptor binding affinity

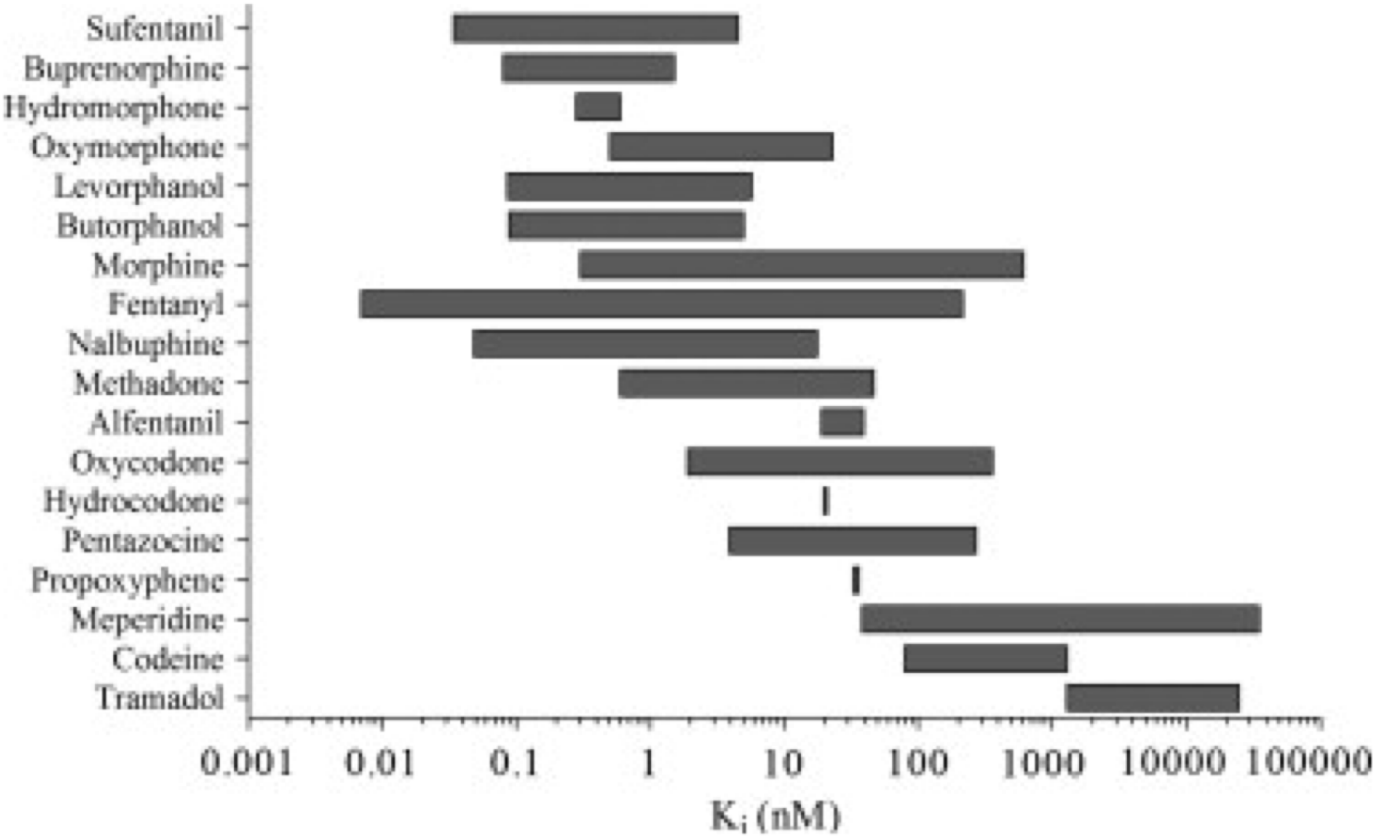


Fig. 4.

Range of literature $K_i$ values for opioid drugs in MOR inhibition assays.

Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology 2011;59(3):385-390

# Mu receptor binding affinity

| Drug | $K_i$ (nM) |
|---|---|
| Sufentanil | 0.1380 |
| Buprenorphine | 0.2157 |
| Hydromorphone | 0.3654 |
| Morphine | 1.168 |
| Fentanyl | 1.346 |
| Methadone | 3.378 |
| Oxycodone | 25.87 |
| Codeine | 734.2 |
| Tramadol | 12,486 |

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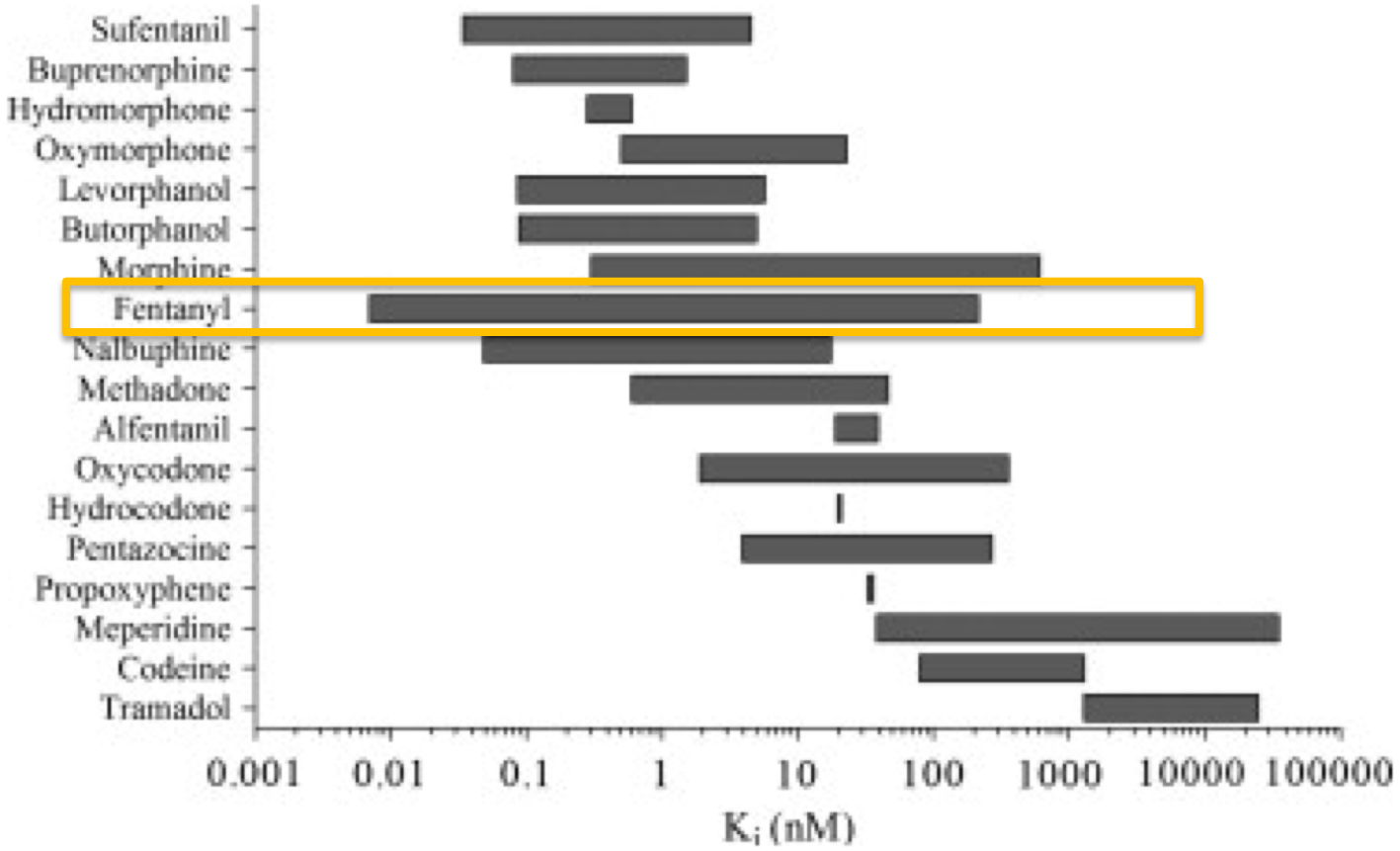


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# How can the risk of precipitated withdrawal be reduced during bup/nx induction?

1. Ensure Clinical Opiate Withdrawal Scale score (COWS) > 12 prior to induction
    - Also ensure a substantial proportion of the COWS score is due to objective withdrawal signs
2. Introduce bup/nx gradually via Butrans patch(es)
    - Gradual absorption of buprenorphine will not cause a “precipitated” withdrawal
3. Use a small initial dose of bup/nx during induction
    - A smaller dose will cause less displacement of other opioids from receptors, and therefore less likely to precipitate withdrawal, or if one occurs likely less severe

# SWITCHING FROM METHADONE TO BUP/NX

# Why Switch From Methadone to Bup/nx?

- Bup/nx has a better safety profile
- Patients who take benzodiazepines or alcohol safer on bup/nx than MMT
- More carried doses with bup/nx may result in better treatment retention
- No evidence that bup/nx prolongs QTC interval

# What method should be used to transition from methadone to buprenorphine/naloxone?

- Depends on time available, stability of patient, and availability of inpatient beds
- Concurrent psychiatric or acute medical issues necessitate inpatient treatment

# Methadone to buprenorphine/naloxone transition protocols:

1. Methadone taper before classic induction
2. Conversion to SROM before bup/nx transition

a) Conversion to hydromorphone before bup/nx transition

3. Butrans Patch assisted
4. Bup/nx Microdosing
5. Fentanyl Patch assisted

# *Method 1: Simple Methadone Taper and Cessation*

- Taper MMT to 30mg daily or less, and then stop MMT for more than 36 hours
- When COWS  score > 12, give bup/nx 2mg SL
  - Reassess COWS 1 hour post-dose
  - Repeat 2 mg at 1 hour if COWS score ≤ pre-dose score
  - If COWS score increases post-dose, evaluate for possible precipitated withdrawal, and if present, hold bup/nx until COWS returns to pre-induction level
  - If there is no precipitated withdrawal, repeat bup/nx 2 mg SL Q1H PRN until comfortable or maximum 12mg on day 1
    - » **Advantage:** Simple method
    - » **Disadvantage:** Prolonged time of MMT taper and associated risk of destabilization

# *Method 2: Use SROM as an Intermediate Maintenance Opioid Before Transition to Bup/Nx*

- Transition stable patient on MMT to SROM using a 1:4 - 1:6 ratio
- Over a few visits, adjust the SROM dose for patient comfort
  - The goal is no withdrawal, and allow SROM to wash out MMT
- Continue SROM for ~4-7 days after MMT has been discontinued to ensure low residual MMT blood levels
- For higher doses of MMT, use a longer washout period on SROM.  Clinicians often treat for a week on SROM.
- Stop the SROM

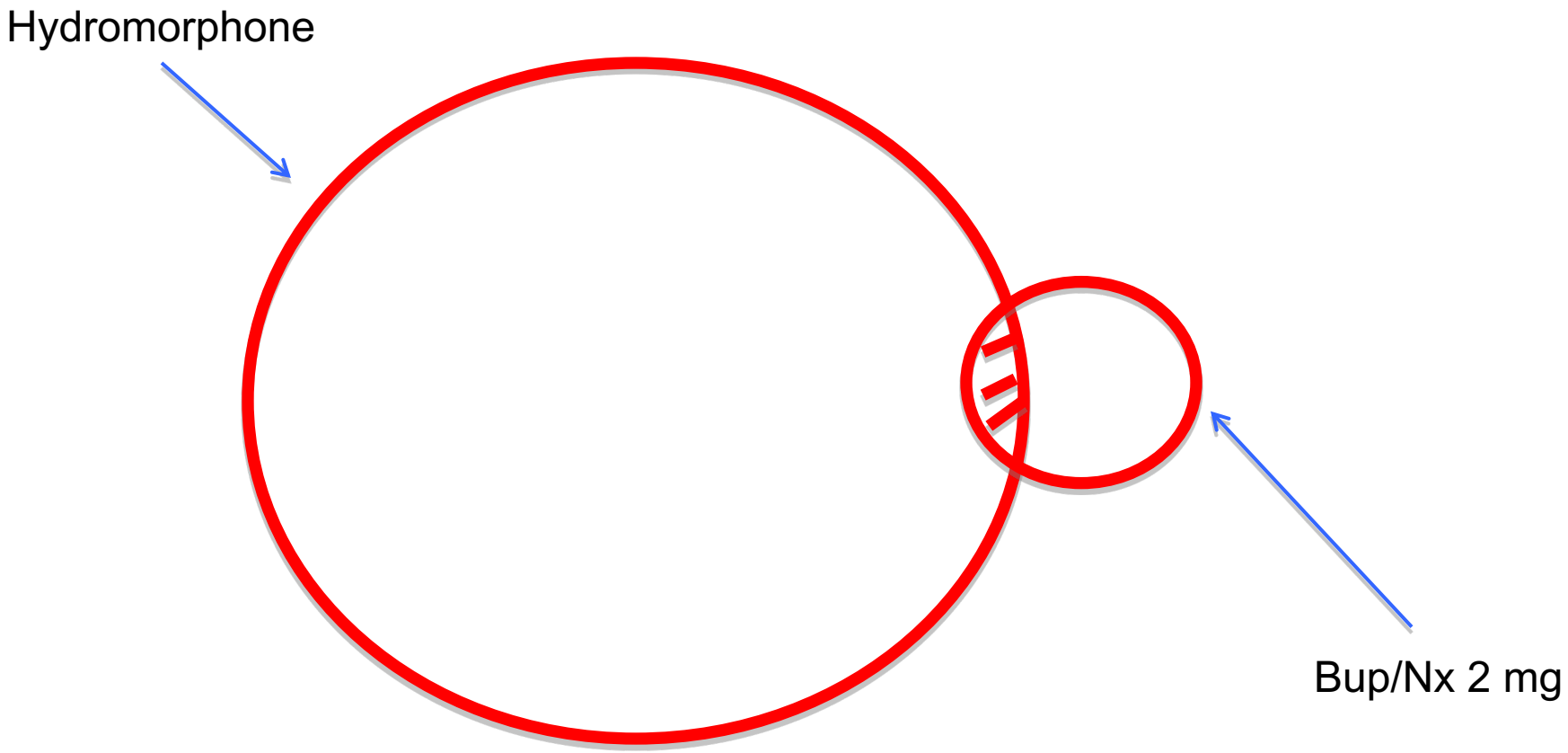
# *Method 2: Use SROM as an Intermediate Maintenance Opioid Before Transition to Bup/Nx*

(continued)

- 24 hours after last SROM, begin serial COWS assessments.
- Remember, SROM is short acting morphine in a delayed release formulation. Thus, after morphine has been absorbed from capsule beads, the half life is 4 hours.
- Once COWS > 12, initiate bup/nx as per the regular protocol

  - **Advantages:** SROM provides more rapid development of withdrawal compared to MMT withdrawal
  - **Disadvantage:** Time to find the right SROM dose

# *Method 2a: Use Hydromorphone as an Intermediate Maintenance Opioid Before Transition to Bup/Nx*



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DOI: 10.1111/j.1521-0391.2011.00159.x

# Transdermal Buprenorphine to Switch Patients from Higher Dose Methadone to Buprenorphine without Severe Withdrawal Symptoms

**Melanie Hess, MD, Lukas Boesch, PhD, Ria Leisinger, MD, PhD, Rudolf Stohler, MD, PhD**

University Department of General and Social Psychiatry, Psychiatric University Hospital, Zurich, Switzerland

- 11 subjects (3F : 8M), aged 22-49, all in methadone maintenance treatment for at least 3 months with a dose between 70 - 100 mg
- At baseline (T-0), subjects took their last methadone dose under supervision
- A buprenorphine patch (35 µg / hr) was applied 12 hours later. No additional medication was given on the first day.
- 2 mg SL bup. at T-48 and T-60 hours
- 8 mg SL bup. at T-72 and T-84 hours
- 8 mg at T-96, T-102, and T-109 hours
- 10/11 Subjects were discharged on day 5 on 24 mg bup./day
- Some mild withdrawal (SOWS) experienced from 24-48 hours
- 81.8% were still on bup. on day 14, and 68.6% after 60 days

# Case Report: High-Dose Methadone Transition to Buprenorphine/Naloxone in an Inpatient with a Prolonged QT Interval

Cortina Sandra MD MPH; Mihic, Tamara BSc(Pharm), ACPR, PharmD; Fennemore, Marie BHB, MBChB, FRANZCP; McLean, Mark MD, MSc, FRCPC

Canadian Journal of Addiction: June 2017
Articles: PDF Only

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**Abstract**

ABSTRACT

Methadone and some psychiatric medications are associated with QT interval prolongation. Buprenorphine/naloxone, a newer medication for opioid use disorder, has a better safety profile than methadone including less QT interval prolongation. Transitioning to buprenorphine/naloxone, however, requires patients undergo an uncomfortable period of withdrawal which may discourage treatment retention in patients with severe opioid use disorder. We describe a case of high-dose methadone transition to buprenorphine/naloxone in order to decrease QT interval length and allow optimization of psychiatric medical therapy. A protocol for transitioning high-dose methadone to buprenorphine/naloxone using slow-release transdermal buprenorphine patch and careful initiation of sublingual buprenorphine/naloxone utilizing the Clinical Opiate Withdrawal Scale for monitoring is described.

# Case: High dose methadone transition to Bup/Nx

- 28 M on MMT 180 mg daily, lowered to 70 mg BID
- Schizophrenia with hx violence; QTC > 500
- Butrans patch 20 mcg/hr 3 hours after MMT 70 mg, and MMT stopped
- 24 hours after last MMT: Bup/nx 1 mg Q2H PRN x4
  - COWS immediately pre-dose and 1 hour post-dose
- Stopped Bup/nx on day 2 after 2$^{nd}$ 1mg dose when post-dose COWS increased by 7 points
- Resumed 1 mg x4 on day 3, followed by 4 mg Q2H PRN to a total 16 mg day 3

# *Method 3: Transition High-Dose MMT to Bup/nx using buprenorphine patch (i.e. Butrans ®) and Small Initial Doses of Bup/nx*

- Appropriate for patients on higher dose MMT
- Discontinue MMT and apply Butrans patch 20 mcg/hr
- Apply patch at time of last MMT or ASAP
- Observe patient for up to 48hrs while subjective withdrawal develops
- 48hrs after last MMT, give bup/nx 1/0.25mg SL Q2H x 4. Measure COWS hourly, immediately pre-dose, and 1 and 2 hours post-dose.
- Hold bup/nx if any post-dose score is ≥ 2 points greater than preceding pre-dose score.

# *Method 3: Transition High-Dose MMT to Bup/nx using buprenorphine patch (i.e. Butrans ®) and Small Initial Doses of Bup/nx*

- If COWS score is rising, stop the induction, and treat with adjuncts for withdrawal such as clonidine, acetaminophen, dimenhydrinate, NSAIDS, quetiapine, and repeat bup/nx 1/0.25mg SL Q2H x 4 the next day
- Once patient can tolerate 4 doses of bup/nx 1/0.25mg without an increase in COWS score greater 2 points, give bup/nx 2-4mg SL Q2H PRN to level of patient comfort or up to 16mg/day
  - **Advantage:** Achieves transition from high-dose MMT to bup/nx with little withdrawal during process, and over a short time
  - **Disadvantage:** Low affinity of methadone gives a higher risk of precipitated withdrawal

# Method 4: Bup/nx Microdosing

- Similar principles to the bup patch induction protocol, but at half the dose (0.5mg)
- Small doses are unlikely to precipitate withdrawal.
- Over time, the partial agonist slowly displaces the full agonist (MMT or a recreational opioid) from the receptor.
- A two case series describes this technique.

# 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 |

Ref: Robert Hämmig, Antje Kemter, Johannes Strasser, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Substance Abuse and Rehabilitation July 2016

# Vancouver area Bup/nx Microdosing schedule

- Canadian tablet formulation doesn't allow following the case series dose schedule

- IMPORTANT: Call the pharmacy in advance to explain the clinical plan, and ask them to cut the 2mg tablets into quarters

- Day 1 | 0.5mg
- Day 2 | 0.5mg
- Day 3 | 1.0mg
- Day 4 | 1.0mg
- Day 5 | 1.5 mg
- Day 6 | 1.5mg
- Day 7 | 2 mg
- Day 8 | 4 mg
- Day 9 | 6 mg
- Day 10 | 8-12 mg
- Day 11 | 16 mg

# Vancouver area Bup/nx Microdosing

- Can be used when transitioning from MMT to bup/nx, or from illicit opioid use to bup/nx
- If the patient is on MMT, continue it until 16mg of bup/nx is achieved, then discontinue MMT
- This technique is not well studied, and there are a wide variety of dosing schedules that individual physicians use
- See patient frequently to reassess
- Dr Rupi Brar will be leading data collection in the evaluation of microdosing in both acute care and community settings (BCCSU/S.Nolan/N.Fairbairn)

# Method 5: Transition High-Dose MMT to Bup/nx Using Fentanyl Patch as Intermediate Maintenance

- Fentanyl has a higher affinity for mu receptor - less likely to be displaced by Bup/nx
- Appropriate for patients on MMT > 30 mg daily
- Stabilize patient on fentanyl patch for 3-7 days to allow MMT to wash out
  - ~3 days for 30-40mg
  - ~4 days for 40-50mg
  - ~5 days for 50-70mg
  - ~6 days for 70-100mg
  - ~7 days for > 100 mg
- Stop MMT and apply fentanyl patch
  - 25 mcg/hr if on methadone 31-40 mg/day, and
  - 50 mcg/hr if on methadone > 40 mg/day

# Method 5: Transition High-Dose MMT to Bup/nx Using Fentanyl Patch as Intermediate Maintenance

- If signs of withdrawal occur earlier than 3-4 days, low dose bup/nx can be tried (if MMT was 30-60mg), or increase fentanyl patch dose and wait (if MMT > 60 mg)
- Additional fentanyl patches Q12H PRN can decrease withdrawal while waiting for MMT to dissociate from receptor; however, the time to peak effect of fentanyl patch is 24-72 hours, so also monitor for opioid toxicity
- If the patient develops opioid toxicity (small pupils, somnolence, decreased RR), remove fentanyl patch and treat opioid toxicity. Observe and wait for mild withdrawal to develop.

# Method 5: Transition High-Dose MMT to Bup/nx Using Fentanyl Patch as Intermediate Maintenance

- **There is slow development of withdrawal after removal of a transdermal fentanyl patch**
- Although IV fentanyl has a very short duration of action due to both rapid elimination and redistribution, the patch is associated with a cutaneous reservoir of fentanyl that delays the development of withdrawal after patch removal
- Fentanyl patch - apparent half-life approximately 21 hours

# Method 5: Transition High-Dose MMT to Bup/nx Using Fentanyl Patch as Intermediate Maintenance

- **On Day 3-7 – remove fentanyl patch and give 2mg bup/nx Q1H PRN**
- Do post dose COWS assessments
- Hold bup/nx if a post-dose COWS is 2 points greater than preceding pre-dose score. Evaluate for precipitated withdrawal.
- If post-dose COWS score increases > 2 points, stop titration for the day, but don't reapply a fentanyl patch. Instead, offer supportive care. Treat with adjuncts such as clonidine, acetaminophen, dimenhydrinate, NSAIDS, quetiapine.
- In general, maximum dose for day one is 8mg
- May titrate up to 16mg on Day 2
  - Advantage: Less risk of precipitated withdrawal due to affinity of fentanyl for mu receptor
  - Disadvantage: Patch diversion

# THANK YOU!