Opioid Agonist Therapy 101: An Introduction to Clinical Practice

Initiation & Maintenance

Erin Knight, MD, CCFP(AM), ISAM
Family Physician, Aboriginal Health and Wellness
Medical Director, Addiction Services - Health Sciences Centre
Addiction Physician, OAT clinic – Beatrice Wilson Health Centre

Disclosure of Commercial Support

- This program has received financial support from ***The College of Physicians and Surgeons of Manitoba*** in the form of ***funding for payment of presenters and organizers.***
- This program has received in-kind support from ***The College of Physicians and Surgeons of Manitoba*** in the form of ***logistical support.***

- **<u>Potential for conflict(s) of interest</u>:**
  - None identified

Faculty/Presenter Disclosure

- **Faculty:** Dr. Erin Knight

- **Relationships with commercial interests:**
- **None**

Learning Objectives

Upon completion of this session the participant should have an understanding of the management of important issues in the maintenance phase of treatment including

- Initiating and dose adjustments
  - buprenorphine/naloxone: classic and microdosing starts
  - methadone
- Managing 'carry' doses
  - buprenorphine/naloxone
  - methadone
- Managing missed doses
  - buprenorphine/naloxone
  - methadone
- Managing vomited doses
- Using, interpreting and responding to urine drug screens
- Managing concurrent substance use
- Treatment of insomnia

Initiating – buprenorphine/naloxone - classic start

- Patient must be in moderate withdrawal (if recent opioid use)
  - Minimum 4-8 hours since last short acting opioid, 24+ hours since last long-acting
  - Assess using COWS: score >= 12 prior to starting
- Day 1 initial dose: 2-8 mg depending on withdrawal severity and opioid tolerance
  - 2-4 mg top-up doses q1h PRN
  - typical outpatient max dose day 1 = 12-16mg
  - consider higher doses if previously on high dose buprenorphine, high opioid tolerance
- Day 2-3 initial dose: total of previous day ± additional 2-4 mg
  - A second dose can be given after 2-4 hours
- Dose can be adjusted daily
  - A stable dose can be reached within 1-4 days

See Handout

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Initiating – buprenorphine/naloxone - an alternate approach: microdosing

Substance Abuse and Rehabilitation

Dovepress
open access to scientific and medical research

Open Access: Full Text Article

CASE SERIES

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

This article was published in the following Dove Press journal:
Substance Abuse and Rehabilitation
20 July 2016
Number of times this article has been viewed

Robert Hämmig[1]
Antje Kemter[2]
Johannes Strasser[2]
Ulrich von Bardeleben[1]
Barbara Gugger[1]
Marc Walter[2]
Kenneth M Dürsteler[2]
Marc Vogel[2]

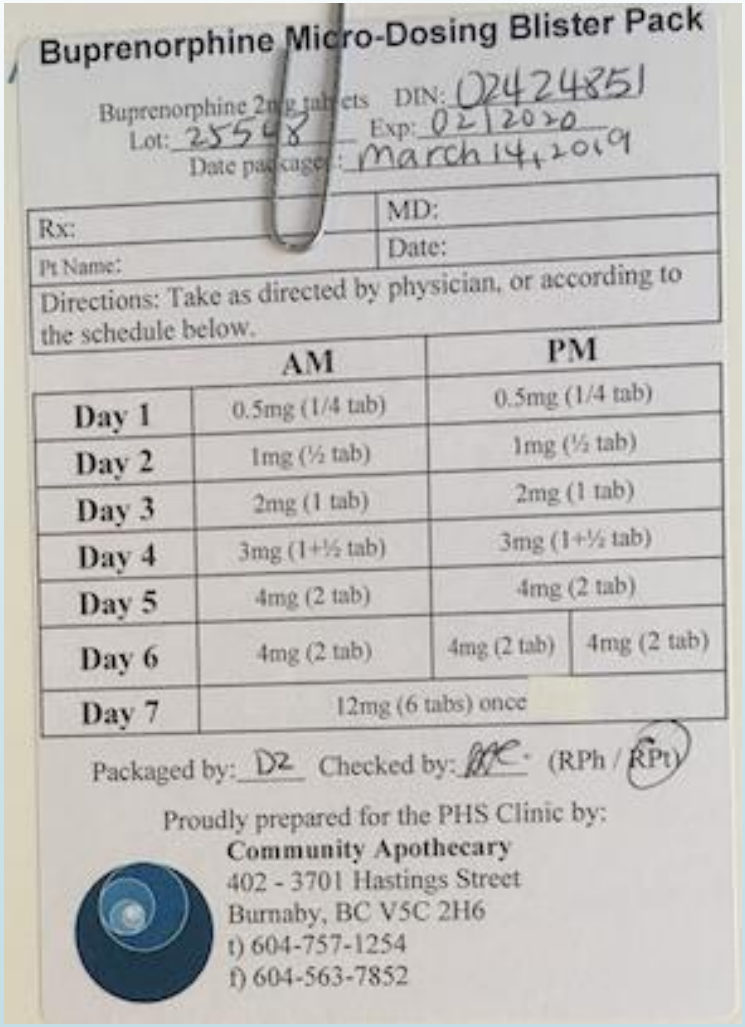
Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Initiating – buprenorphine/naloxone - an alternate approach: microdosing

Day	Order	Number of tablet(s) per dose when using buprenorphine-naloxone 2 mg – 0.5 mg tablet
1	buprenorphine 0.5 mg – naloxone 0.125 mg sublingual BID	One quarter tablet
2	buprenorphine 0.5 mg – naloxone 0.125 mg sublingual TID	One quarter tablet
3	buprenorphine 1 mg – naloxone 0.25 mg sublingual BID	One half tablet
4	buprenorphine 2 mg – naloxone 0.5 mg sublingual BID	1 tablet
5	buprenorphine 2 mg – naloxone 0.5 mg sublingual QID	1 tablet
6	buprenorphine 4 mg – naloxone 1 mg sublingual TID	2 tablets
7	buprenorphine 12 mg – naloxone 3 mg sublingual daily	Refer to MAR for directions

Advise patient to dissolve tablet completely under tongue which can take up to 10 minutes.
While the tablet is dissolving **DO NOT** swallow saliva or pill, and do not talk or drink

Initiating – buprenorphine/naloxone - an alternate approach: microdosing



Buprenorphine Micro-Dosing Blister Pack

Buprenorphine 2mg tablets DIN: 02424851
Lot: 25548 Exp: 02/2020
Date packaged: March 14, 2019

Rx:	MD:
Pt Name:	Date:
Directions: Take as directed by physician, or according to the schedule below.	

	AM	PM	
Day 1	0.5mg (1/4 tab)	0.5mg (1/4 tab)	
Day 2	1mg (½ tab)	1mg (½ tab)	
Day 3	2mg (1 tab)	2mg (1 tab)	
Day 4	3mg (1+½ tab)	3mg (1+½ tab)	
Day 5	4mg (2 tab)	4mg (2 tab)	
Day 6	4mg (2 tab)	4mg (2 tab)	4mg (2 tab)
Day 7	12mg (6 tabs) once		

Packaged by: D2 Checked by: MC (RPh / RPt)

Proudly prepared for the PHS Clinic by:
Community Apothecary
402 - 3701 Hastings Street
Burnaby, BC V5C 2H6
t) 604-757-1254
f) 604-563-7852

Dose Adjustments – buprenorphine/naloxone

- As dose increases, duration without withdrawal increases & cravings decrease
- Balance prevention of withdrawal, cravings and illicit use vs. avoidance of side-effects
  - Avoid dose increases for seeking sedative effect, treated co-occurring disorders (ex. anxiety, PTSD, chronic pain)
- Usual dose: 8-24mg
- In the first week, increase dose by 2-4mg increments daily
- Later adjustments allow 3-7 days between dose increases
- Stability achieved much more quickly than with methadone, often within 1 week
- Doses > 24 mg are sometimes needed, up to 32mg

Initiating – methadone

Start LOW & Go SLOW - first 3-5 days

Opioid tolerance	Methadone starting dose
Low, including recent abstinence	10mg or less
Moderate, or high but risk factors for methadone toxicity	20mg or less
High, no risk factors for methadone toxicity	30mg or less

Max starting dose is 30mg

Initiating – methadone

Start LOW & Go SLOW – The First 2 Weeks

- Assess for dose increases once or twice weekly
  - 5-10 mg q 3 to 5 days
  - If recent abstinence or high risk of toxicity: increase by 5mg or less q 5-7 days
- The highest risk for overdose is in the first 2 weeks on methadone
  - 6.7x higher risk of OD than the heroin addict NOT in treatment
- The goal is to reach a dose which lasts 24 hours
- Much longer titration to target dose than with buprenorphine/naloxone

Dose Adjustments – methadone

- *As dose increases, duration without withdrawal increases & cravings decrease*
- *Balance prevention of withdrawal, cravings & illicit use vs. avoidance of side-effects*
  - *Avoid dose increases for seeking sedative effect, treated co-occurring disorders (ex. anxiety, PTSD, chronic pain)*
- Usual dose: 60-120mg
- Initially, increase dose by 5-10mg Q 5-7 days
- As the dose effect gets closer to lasting 24 hours, or over 60 mg, slow down the dose increases to 3-5mg Q 5-7 days
- Doses > 120mg are sometimes needed
  - ECG to check QTc
  - Consider peak: trough
- Peak: trough > 2 = rapid metabolizer
  - may be idiopathic or medication related: ARVs, dilantin, rifampin
  - Consider split dose

Managing "carry" doses – buprenorphine/naloxone

- New guidance, hot off the press August 2019!!
  - https://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/Opioid%20Prescribing%20WG/Buprenorphine%20naloxone%20take%20home%20dosing%20draft%20section%20Aug%2021%202019.pdf
- **Buprenorphine is NOT methadone** – safety profile much better = carries are safer
- General principles
  - Daily witnessed dosing until clinical stability demonstrated
    - Stable dose, infrequent missed doses, UDS supportive, regular follow-up, safe storage
  - Weigh benefits of more flexible dosing vs. risks of diversion
- Most common scenario:
  - one additional carry dose every 2 weeks until weekly dispense
  - After further 3 months stability, transition to q2 week dispense
  - After 1 year stability, transition to monthly dispense
- Reassess continually, if destabilization occurs, increase frequency of dispensing

Managing “carry” doses - methadone

- All patients start with daily witnessed dosing
- Take - home doses can be given when
  - At least 2 months in treatment
  - *Clinical Stability* is demonstrated
    - Dose stable, UDS consistent with substance use disorders in remission
    - Psychosocial stability (emotional, psychological, housing, family life…)
    - Adhering to treatment agreement, attending follow-ups…
  - Client is able to store medication safely in a locked box
  - Increased by 1 carry dose every 3-4 weeks, up to maximum 6 carries/week
- Continual reassessment
- Must consider patient safety & public safety when deciding to give carries

Managing missed doses – buprenorphine/naloxone

- Missed doses can indicate a variety of problems including relapse to drug or alcohol use or social instability
- Pharmacists should report missed doses to the physician or clinic promptly
- Due to the partial agonist effect & lower risk of overdose, dose adjustment after missed doses does not require the same degree of vigilance as with methadone
- Missed doses should be reported to the prescriber
- Patient assessment for stability should be carried out and reasons for missed doses explored
- 5 missed doses = Rx cancelled
- Patient should be assessed & dose should be reduced to (ex. 50% of previous dose or 8 mg)
  - if using other opioids, assess COWS to avoid precipitated withdrawal with restart
- 6 or more missed doses – reassess & restart induction process

Managing missed doses – methadone

- Missed doses can indicate a variety of problems including relapse to drug or alcohol use or social instability
- Pharmacists should report missed doses to the physician or clinic promptly
- 1 or 2 missed doses – continue same dose provided they are not intoxicated
- 3 or more missed doses = Rx cancelled
  - Loss of tolerance in as little as 3 days
  - Doses < 30mg
    - After reassessment, can either continue at same dose or reduce dose
  - Doses > 30mg
    - Decrease by 50% or to starting dose (ex. 30mg), whichever is higher
    - If daily assessment possible, may increase by up to 5-10mg daily
    - If daily assessment not possible, or if unstable or using other sedatives, increase dose more slowly
- 4 or more missed doses = reassess and restart

Managing vomited doses

- No replacement unless the emesis was directly witnessed by a professional
- Exception might be in pregnancy
- If vomiting within 15 min. consider replacing 50-75% of the dose
- If vomiting within15–30 min. consider replacing 25-50% of dose
- Consider pre-treated for nausea prior to replacement
- Observe for further nausea & for sedation for at least 30 min. after replacement dose

Using, interpreting and responding to urine drug screens

- Why?
  - Corroborates history provided by the client
    - At admission to document opioid use
    - During stabilization to monitor progress
    - During maintenance to monitor stability and facilitate carry doses
  - Confirms stability or identifies relapse
- How?
  - Random UDS preferred
  - Measures to prevent tampering
    - Leave bags, bulky clothes, empty pockets
    - Bathroom with 'blued' toilet, no access to warm tap water
    - Temperature strip on bottle
  - Point of care VS. lab-based immunoassay VS. GC-MS (comprehensive)

Using, **interpreting** and responding to urine drug screens

- What we're looking for
  - Methadone (MTD) & methadone metabolites (EDDP)
    - To ensure it's there, (particularly if carry doses)
  - Opioids (MOP, OXY, FEN)
    - To check if it's there
  - Other substances – polysubstance use is the norm
    - Cocaine (COC), Amphetamines (AMP), Methamphetamines (MET)
    - Benzodiazepines (BZO)
    - Marijuana (THC)
    - Other sedatives
      - Alcohol, gabapentin, OTCs (diphenhydramine)
      - Sedative effect, important to identify
      - not identified on immunoassay. will show up on comprehensive GC/MS

Using, **interpreting** and responding to urine drug screens

- What the results mean:
  - Benzodiazepines and cannabinoids may persist in urine for several weeks
  - All other substances typically clear within 1-4 days
  - Clonazepam is NOT reliably detected on benzodiazepine immunoassay (POC or lab-based)
    - is detected on GC-MS (comprehensive)
  - Diazepam breaks down to tempazepam and oxazepam
  - Fentanyl, carfentanyl, oxycodone and all synthetic opioids are NOT reliably detected on the MOP/opiate immunoassay, require separate tests
  - False positives are possible
    - amphetamines/methamphetamines
      - Ranitidine, pseudoephedrine, bupropion, venlafaxine
    - MOP/opiates
      - Poppy seeds, quinolones
  - False negatives also occur
    - If results from POC or immunoassay are unexpected, send for GC-MS and/or call the lab
  - Buprenorphine is NOT reliably detected currently on GC-MS/comprehensive (in MB)

Using, interpreting and **responding** to urine drug screens

- Discuss UDS results inconsistent with reported use
  - Consider false positives and false negatives
  - Send for comprehensive when discordant results
- Consistent UDS + for opioids may reflect sub-therapeutic dosing
- Relapses are common and part of recovery – discuss openly to help with relapse prevention planning
- If ongoing opioid or other substance use, remove carries (if present)
  - If inability to provide UDS, consider it + for something
- If urine is cold
  - did they bring it with them?
  - Did they dilute it?
- If negative for prescribed buprenorphine/methadone
  - Confirm by comprehensive, if confirmed negative
    - Remove carries
    - ? Discontinue prescribing

Managing concurrent substance use

- Counseling, mutual support groups, residential treatment
- Pharmacotherapy
  - Alcohol
    - Acamprosate for relapse prevention
  - Nicotine
    - Nicotine replacement
    - Varenicline
    - Bupropion
  - Benzodiazepines
    - Long-term gradual taper, dispensed with OAT – discussed elsewhere

Insomnia

- Difficulties with sleep are common
- The goal is to manage this without the use of potentially addictive sedatives
- During stabilization phase withdrawal symptoms cause disturbed sleep
  - Clonidine 0.1 mg HS can be helpful, not for ongoing use
- 'Sleep hygiene' - life is often chaotic when using - establishing regular routines has to be learned
- PTSD – Prazosin is helpful for reduction in nightmares (off label use)
- Quetiapine in low doses 25-50mg is often used as a non-addictive night sedation (off label use), or trazodone 50-100mg (off label use)

References

- Buprenorphine/naloxone for Opioid Dependence- Clinical Practice Guideline CAMH: principle author Curtis Handford
- Manitoba Methadone & Buprenorphine Maintenance Recommended Practice 2015
- Methadone Maintenance Treatment Program Standards & Clinical Guidelines The College of Physicians & Surgeons of Ontario 2011
- 'No Evidence to Support QTc Interval Screening in MMT' – Cochrane Review of 20 June 2013 - Addiction Treatment Forum 19th July 2013
- CPSM Buprenorphine/naloxone recommended practice manual. Take home (carry) dosing recommendations. DRAFT August 2019.
- A Guideline for the Clinical Management of Opioid Use Disorder. BCCSU and BC Ministry of Health. June 5, 2017.