Managing OUD: Buprenorphine/naloxone

Vancouver Inner-City Medicine Review Conference 2019

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Heatley Community Health Centre & DTES Connections

Faculty/Presenter Disclosure

- Relationships with financial sponsors:
  - None
- Disclosure of Financial Support
  - None
- Mitigating Potential Bias
  - Use generic names
  - Flag off-label utilization and include references

The Basics

KEY POINTS

- Opioid use disorder is often a chronic, relapsing condition associated with increased morbidity and death; however, with appropriate treatment and follow-up, individuals can reach sustained long-term remission.
- This guideline strongly recommends opioid agonist treatment with buprenorphine–naloxone as the preferred first-line treatment when possible, because of buprenorphine's multiple advantages, which include a superior safety profile in terms of overdose risk.

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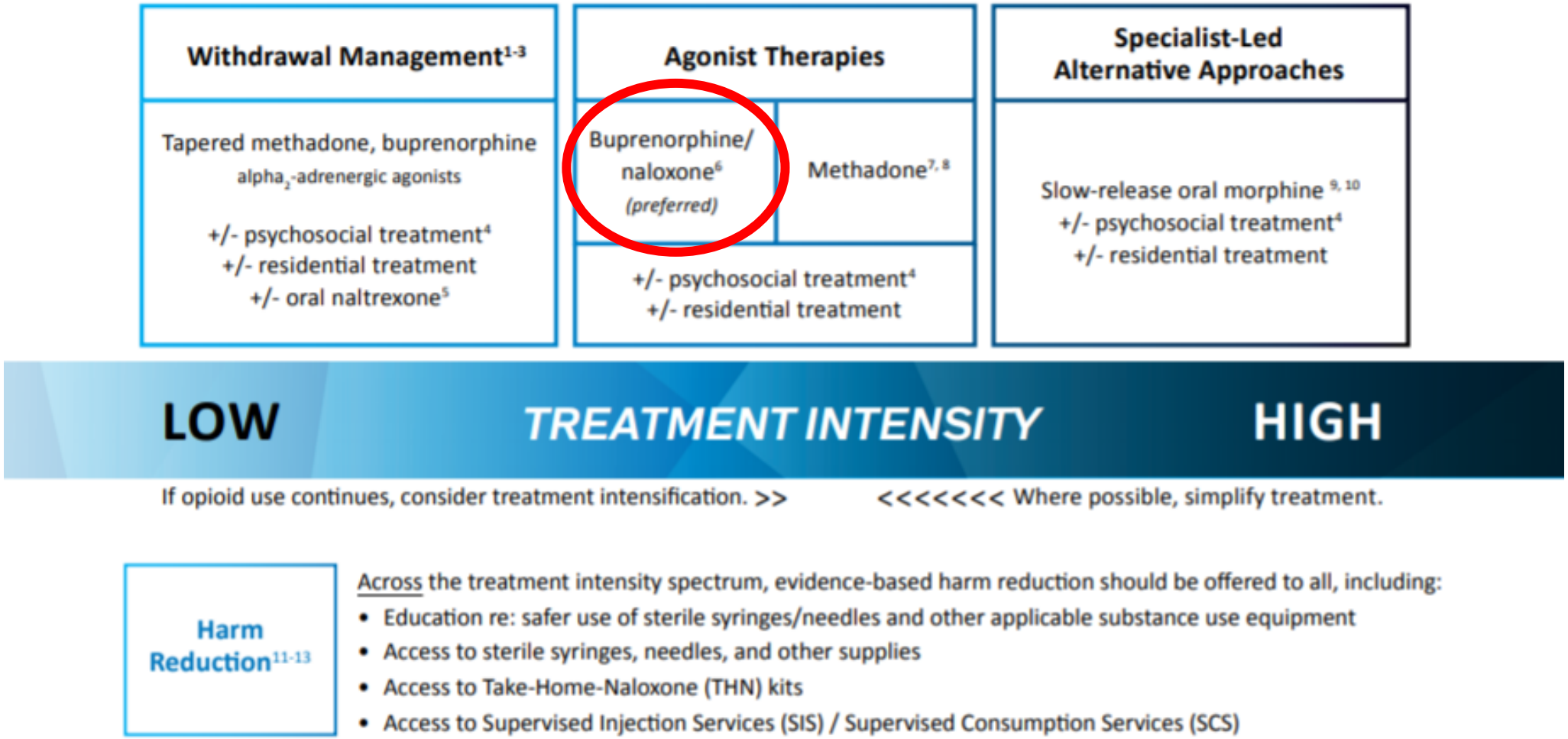
Figure 2. Clinical management of opioid use disorder



https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf

PART 1: B.C. CORONERS SERVICE REVIEW FINDINGS

This report includes general statistical information of 1,854 overdose deaths occurring between January 1, 2016, and July 31, 2017, as well as a more detailed comparative review of 615 deaths over two time periods (March 1- May 31, 2016, and March 1- May 31, 2017) **'the comparative sample'**. The purpose of comparing these two specific time periods was to determine if there were changes over time based on the geographic or physical location, decedent drug use characteristics or changes in toxicology findings.

The 615 overdose deaths in the comparative sample represent 33% of all illicit drug overdose deaths occurring from January 1, 2016, to July 31, 2017.

Suboxone (Buprenorphine and Naloxone) Prescription

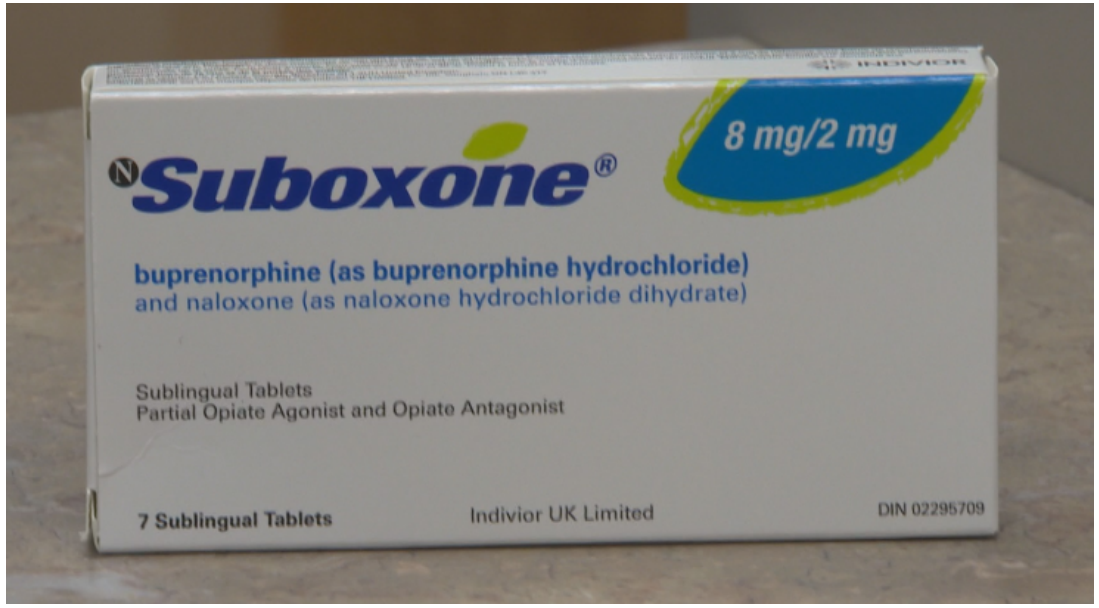
This review found no decedents with buprenorphine present on toxicology tests. This is consistent with the evidence demonstrating the safety of buprenorphine/naloxone and the role this medication in preventing overdose deaths.

https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/death-review-panel/bccs_illicit_drug_overdose_drp_report.pdf


First
line
Second
line


SOAP

- Partial-agonist
- High binding affinity
- “ceiling effect”



naloxone

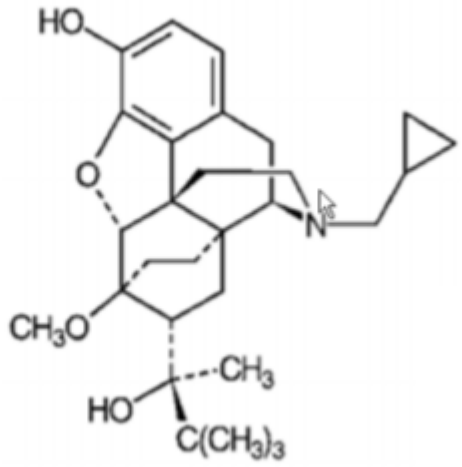
Naloxone is an antagonist at mu, delta, and kappa-opioid receptors. Because of its almost complete first pass metabolism and low sublingual bioavailability, naloxone administered orally or sublingually has no detectable pharmacological activity. However, if misused or abused intranasally or by injection by a person dependent upon a full opioid agonist, the presence of naloxone in SUBOXONE® can produce marked opioid antagonist effects that can prompt the immediate onset of opioid withdrawal symptoms as a deterrent to misuse and abuse.

- Average elimination ½ life = 37hrs (range 24-69hrs)

-Up to 12mg (?16) on day 1

-Max dose 24mg (32mg in U.S. labelling)

Structural formula:



CONTRAINDICATIONS

SUBOXONE® sublingual tablet is contraindicated in:

- Patients who are hypersensitive to buprenorphine, naloxone, or to any ingredient in the formulation (For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).
- Opioid naïve patients.
- Patients with severe respiratory insufficiency: e.g., acute or severe bronchial asthma, chronic obstructive airway, status asthmaticus, acute respiratory depression, and/or cor pulmonale.
- Patients with severe hepatic impairment.
- Patients with acute alcoholism or delirium tremens and convulsive disorders.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis). Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

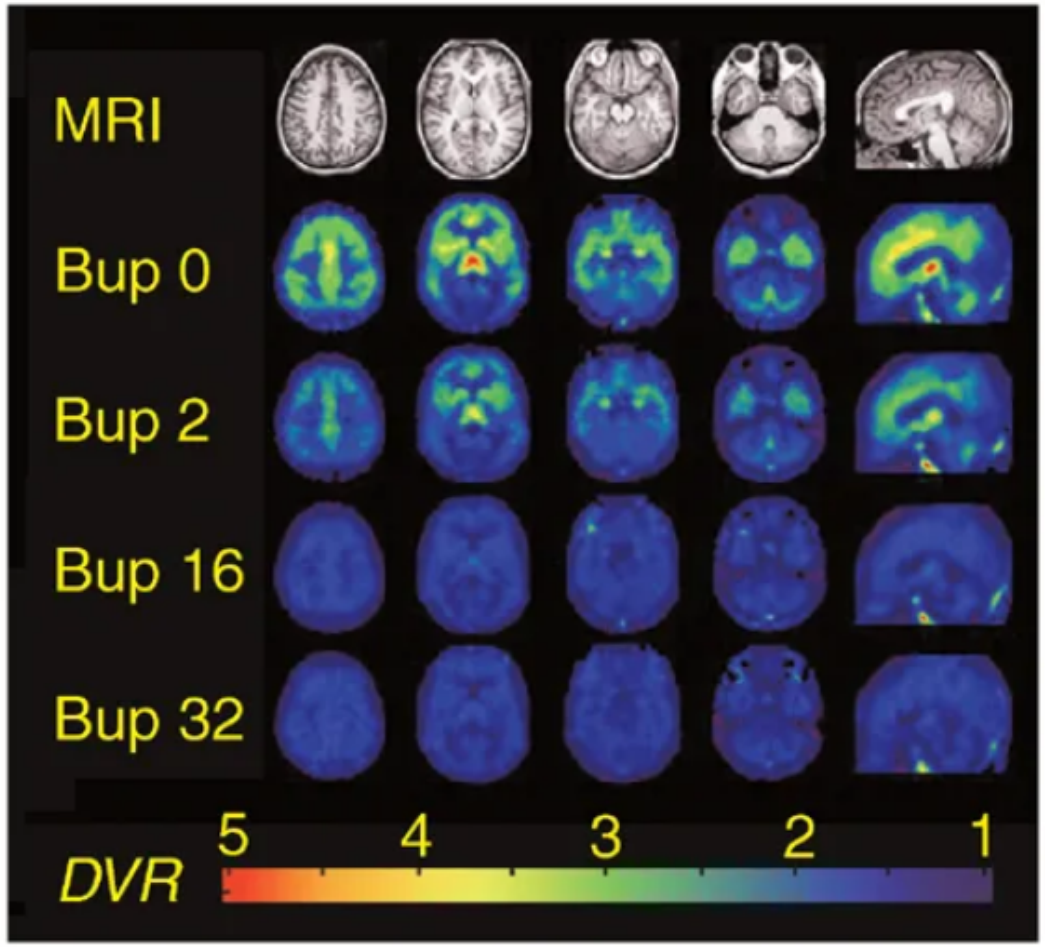
Appropriate security measures should be taken to safeguard stocks of SUBOXONE® against diversion.

SUBOXONE® must be dispensed on a daily basis under the supervision of a healthcare professional until the patient has sufficient clinical stability and is able to safely store SUBOXONE® take-home doses.

	B_{max}/K_d	Percentage changes from BUP placebo			Dose
Brain region	**BUP 0 mg**	**BUP 2 mg**	**BUP 16 mg**	**BUP 32 mg**	**F(2,8)**
Whole brain	0.69 (0.01)	40.6 (7.9)	80.2+(2.2)	84.1 (1.6)	F=41.4
Prefrontal cortex (BA 10)	1.19 (0.03)	46.9 (8.7)	89.5 (2.6)	96.2 (1.8)	F=41.0
		48.1 (6.4)	*87.7 (5.0)*		
Subgen. ant. cing. (BA 25)	1.39 (0.04)	45.5 (8.9)	91.5 (2.9)	98.4 (1.1)	F=45.8
		48.9 (0.7)	*85.4 (2.8)*		
Rostral ant. cing. (BA 32)	1.56 (0.04)	44.3 (9.6)	89.7 (3.1)	97.0 (1.6)	F=38.0
		42.7 (2.9)	*85.2 (2.4)*		
Caudate	1.90 (0.15)	40.2 (10.6)	87.3 (4.3)	95.5 (1.8)	F=39.0
		39.9 (4.5)	*84.4 (3.3)*		
Nucleus accumbens	2.09 (0.12)	36.5 (8.9)	85.7 (3.0)	93.8 (2.0)	F=62.9
		40.3 (3.5)	*81.6 (4.2)*		
Thalamus	1.84 (0.08)	36.1 (7.7)	79.5 (2.7)	88.5 (1.1)	F=55.5
		37.3 (5.4)	*78.9 (1.9)*		
Amygdala	1.57 (0.08)	27.0 (8.6)	85.4 (2.3)	96.1 (1.6)	F=75.7
		35.1 (3.5)	*84.1 (1.4)*		

Neuropsychopharmacology **volume 28**, pages2000–2009 (2003)

Figure 3



Parametric images of μOR availability (B_{max}/K_d; extracted from Logan plot slopes with the occipital cortex as the input function) from a representative heroin-dependent volunteer (#7500; see Figure 2) during daily maintenance on BUP placebo (row 2), 2 mg (row 3), 16 mg (row 4), and 32 mg (row 5). Images are scaled so that binding in the occipital cortex, an area devoid of μ receptors, is equal to 1. Four transverse sections (from superior (column 1) to inferior (column 4)) and one sagittal section (column 5) are shown, which correspond to T1-weighted anatomical MRI images (row 1). The pseudocolor scale depicts DVR values from 1 to 4.

Goals

An effective maintenance dose:

- eliminates withdrawal symptoms for more than 24 hours
- blocks the euphoric effects of opioids
- reduces or eliminates drug craving
- does not induce excess sedation

- Prevents withdrawal for 24+ hours
- Reduces Cravings to manageable level
- Supports substance use goals

- Does NOT cause intolerable side effects

Case

- JA is a 32 year old male with long-standing OUD (1/2 gram fentanyl IV daily)
- Presents to clinic at 2pm requesting to start suboxone

❑Normal use pattern (amount, frequency, route)

❑Time and amount of last use

❑UDS

❑Pharmanet review

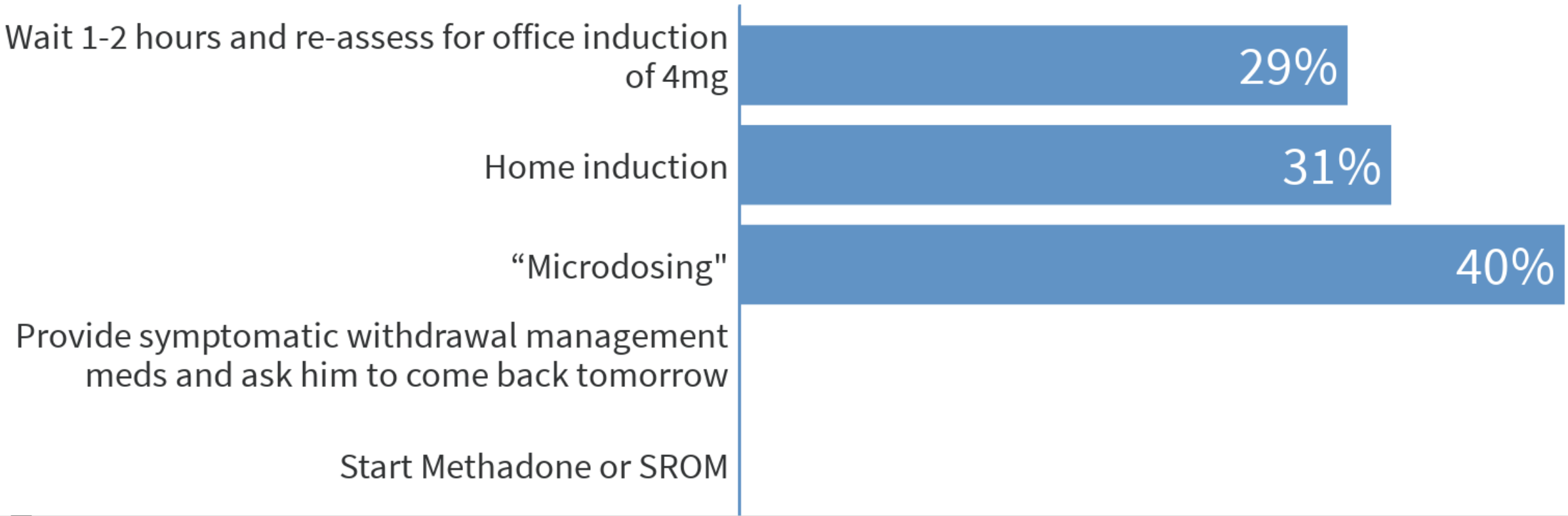
❑COWS score

❑Subjective description of current state

History and Assessment

- Last used ~ 14 hrs ago ; 1 pt IV
- UDS Positive for fentanyl, benzos, amphetamines
- Pharmanet shows antibiotics 3/12 ago
- COWS = a “soft 10”
- States he feels ‘pretty dopesick’, but not visibly distressed

JA, a 32 year old male with longstanding OUD (1/2 gram fentanyl IV daily), presents at clinic at 2pm requesting to start suboxone. What option do you choose?



Induction

- 1) Textbook/traditional office based-induction
  - COWS > 12
  - 6-12 hrs since last opioid use
  - 4mg SL , repeat q 60-120 mins

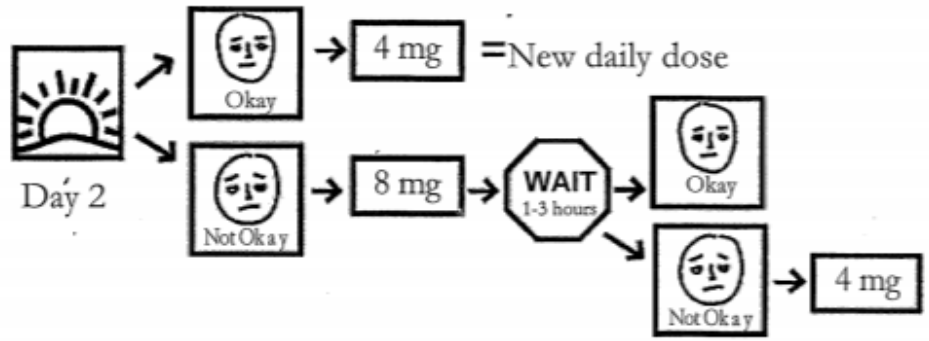
- *Editorial Comments*

Induction

- 2) Home Induction

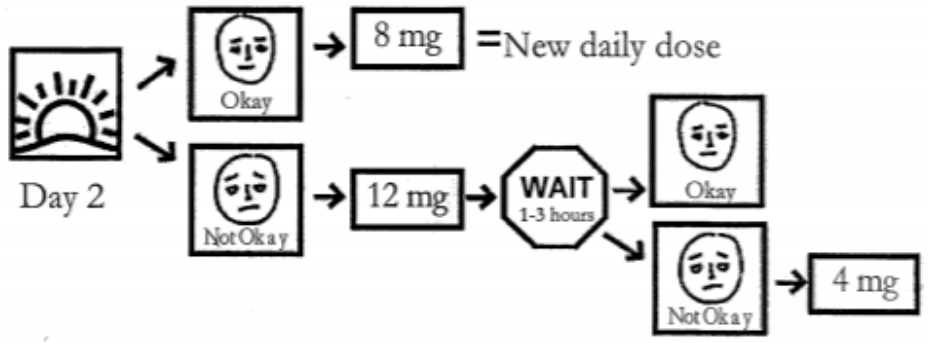
If the total on Day One was

4 mg



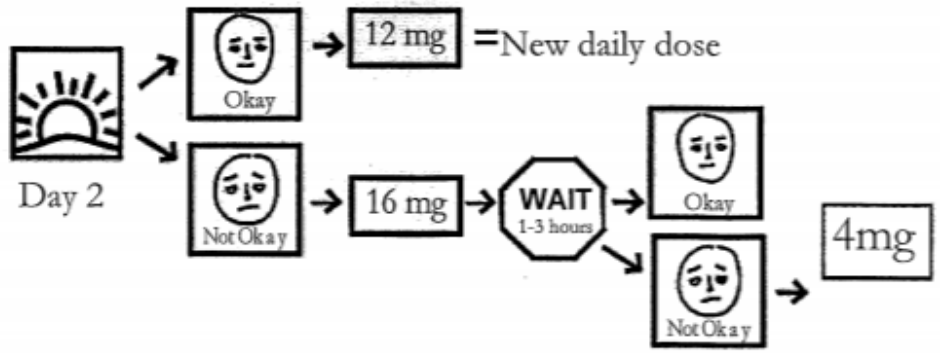
If the total on Day One was

8 mg



If the total on Day One was

12 mg



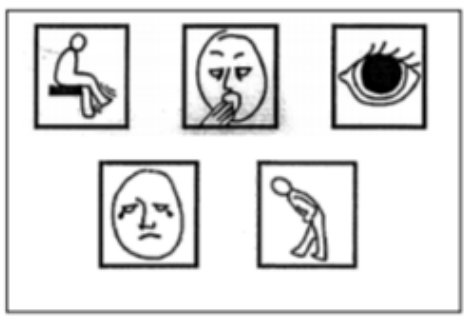
	Time	Amount	
1st Dose			= Total mg taken on Day One
2nd Dose if needed			
			= Total mg taken on Day Two

Still feel really bad?
Call your doctor at _____

When to Take Your First Dose of Suboxone:

- In order for suboxone to work and not make you feel much sicker ("precipitated withdrawal") you want to feel lousy from your withdrawal symptoms before you take your first dose.
- It should be **at least 12 hours since you last used heroin** or pain pills (oxycontin, dilaudid, T3 etc)
- It should be at least 24 hours since you last used methadone/kadian or other long acting downers/opioids
- Wait it out as long as you can. The worse you feel when you begin the medication, the better it will make you feel and the more satisfied you will be with the whole experience
- You should have at **least 3 of the following** feelings when you take your first dose:

  - ☐ Twitching, tremors or shaking
  - ☐ Joint and bone aches
  - ☐ Bad chills or sweating
  - ☐ Anxious or irritable
  - ☐ Goose bumps
  - ☐ Very Restless, can't sit still
  - ☐ Heavy Yawning
  - ☐ Enlarged Pupils
  - ☐ Runny Nose, tears in eyes
  - ☐ Stomach cramps, nausea, vomiting or diarrhea



Taking the pill:

- Put the tablet under your tongue and keep it there
- **If you swallow the pill it does not work** and will have no effect!
- It takes between 3-10 minutes for the tablet to dissolve and be absorbed fully through your mouth—don't swallow during this whole time!
- You should start feeling better in about 30-45 minutes, but it will continue to increase in effect for the next 1-3 hours

Induction

- 3) Microdosing

Subst Abuse Rehabil. 2016; 7: 99–105.
Published online 2016 Jul 20. doi: 10.2147/SAR.S109919
PMCID: PMC4959756
PMID: 27499655

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

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

DTC Recommended Suboxone Microdosing Protocols:

OPTION 1 (faster)	**Option 2** (slower)
Day 1: 0.5mg	Day 1: 0.5mg
Day 2: 0.5mg BID	Day 2: 0.5mg
Day3: 1mg BID	Day 3: 1mg
Day 4: 2mg BID	Day 4: 1.5mg
Day 5: 3mg BID	Day 5: 2mg
Day 6: 4mg BID	Day 6: 2.5mg
Day 7:12mg once	Day 7: 3mg
Total: 33.5mg	***Total: 11mg***

Miss 1 day:

Repeat the previous day and continue

e.g. Has Day 1, 2 and 3…misses day 4 (2mg BID)→ repeat Day 3 (1mg BID) and then continue

Miss 2 days:

Need to r/a and /or re-start

Options:

1) May provide as 7 day "take home" blister pack **(will require 24hr pharmacy prep time)**
2) May provide as "1st dose witnessed, 2nd dose carry x 7 days"
3) May provide as DWI, as usual, for Option 2

Optional:

1) May also start Methadone or Kadian simultaneously; and titrate as needed [*Kadian preferred due to shorter ½ life and easier to transition to full dose suboxone]*

OPTION 1 (faster)

Day 1: 0.5mg

Day 2: 0.5mg BID

Day3: 1mg BID

Day 4: 2mg BID

Day 5: 3mg BID

Day 6: 4mg BID

Day 7:12mg once

Total: 33.5mg

Option 2 (slower)

Day 1: 0.5mg

Day 2: 0.5mg

Day 3: 1mg

Day 4: 1.5mg

Day 5: 2mg

Day 6: 2.5mg

Day 7: 3mg

Total: 11mg

…back to JA

Missed Doses

DCHC/Connections Suboxone Missed Dose Protocol

1) Missed Doses and using opiates:

-needs to go through induction process again!

-even after 2 days of missed suboxone,- as at risk of precipitated withdrawal if give suboxone while any opiates are on board

2) Missed Doses and NOT using opiates:

consider rapid UDS to confirm

Missed dose protocol AND NOT USING ANY OPIATES

-no systematic review evidence of any ideal protocol
-missed dose causes loss of tolerance
-Assuming daily dosing, if ≤ or = 5 days doses missed, resume same dose.
-Otherwise refer to table below

Bupenorphine dose	# consecutive days missed	New starting dose
>8 mg	>7d	4 mg
>8 mg	6-7 d	8 mg
6-8 mg	6 or more d	4 mg
2-4 mg	6 or more d	2-4 mg

Buprenorphine “PRN” ?

Buprenorphine and Pregnancy

ORIGINAL ARTICLE

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O'Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

Parallel with evidence supporting the safety and effectiveness of buprenorphine/naloxone, pregnancy was recently removed as a contraindication in the product monograph of the Health Canada-approved buprenorphine/naloxone (brand name Suboxone®).[43-47] In view of these developments, initiation of buprenorphine/naloxone treatment may be considered on a case-by-case basis by the treating clinician with appropriate monitoring.

In cases where patients have achieved clinical stability on buprenorphine/naloxone prior to pregnancy, continuation of this treatment is recommended.[5] Transition to buprenorphine monotherapy during pregnancy is not necessary, but may be offered to a patient who is fully informed of treatment options and wishes to proceeded with buprenorphine.