Induction Without Withdrawal: Buprenorphine/Naloxone Micro-Dosing

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James Wong, BSc

Disclosure Information

- Presenter 1: Pouya Azar, MD, FRCPC, DABAM
  - No Disclosures
- Presenter 2: Nickie Mathew, MD, MSc, FRCPC, ABPN, ABPM
  - No Disclosures
- Presenter 3: James Wong, BSc
  - No Disclosures

~1 minute video of patient discussing precipitated withdrawal

Learning Objectives

- Learn about buprenorphine/naloxone micro-induction in the outpatient setting.
- Learn about rapid buprenorphine/naloxone micro-induction in the inpatient setting.
- Learn about rapid micro-induction onto buprenorphine extended-release.

Reference 1

Fatal dose of fentanyl
(2 mg or 2000 mcg)

Fatal dose of carfentanil
(0.02 mg or 20 mcg)

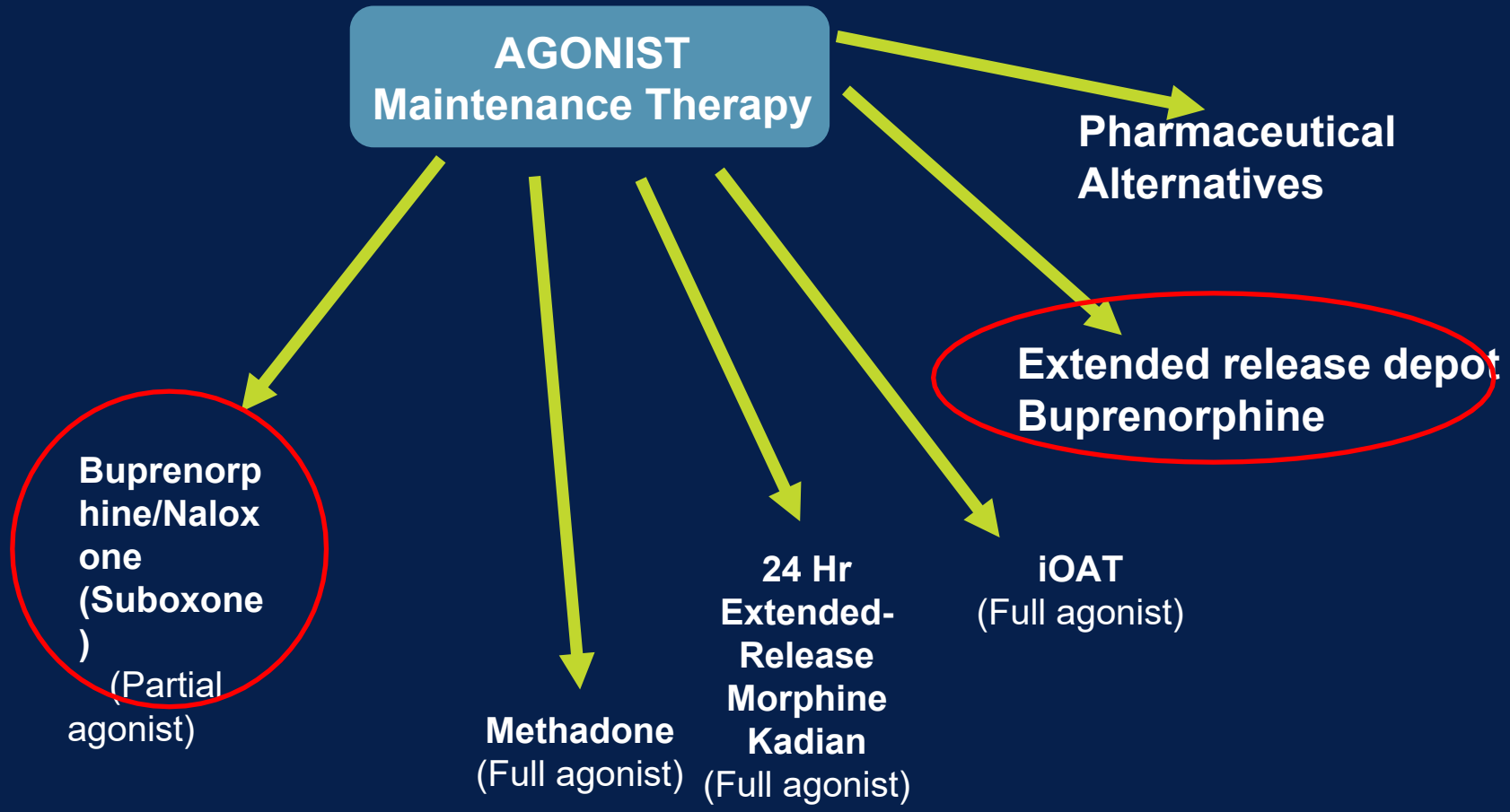
Reference 2

Fentanyl & Fentanyl Analogs

- Fentanyl and its analogs increasingly prevalent
- Difficulty with traditional buprenorphine/naloxone inductions in patients using illicit fentanyl
  - Need longer time for the withdrawal period

References: 3-5

Opioid Use Disorder Pharmacological Tx Options



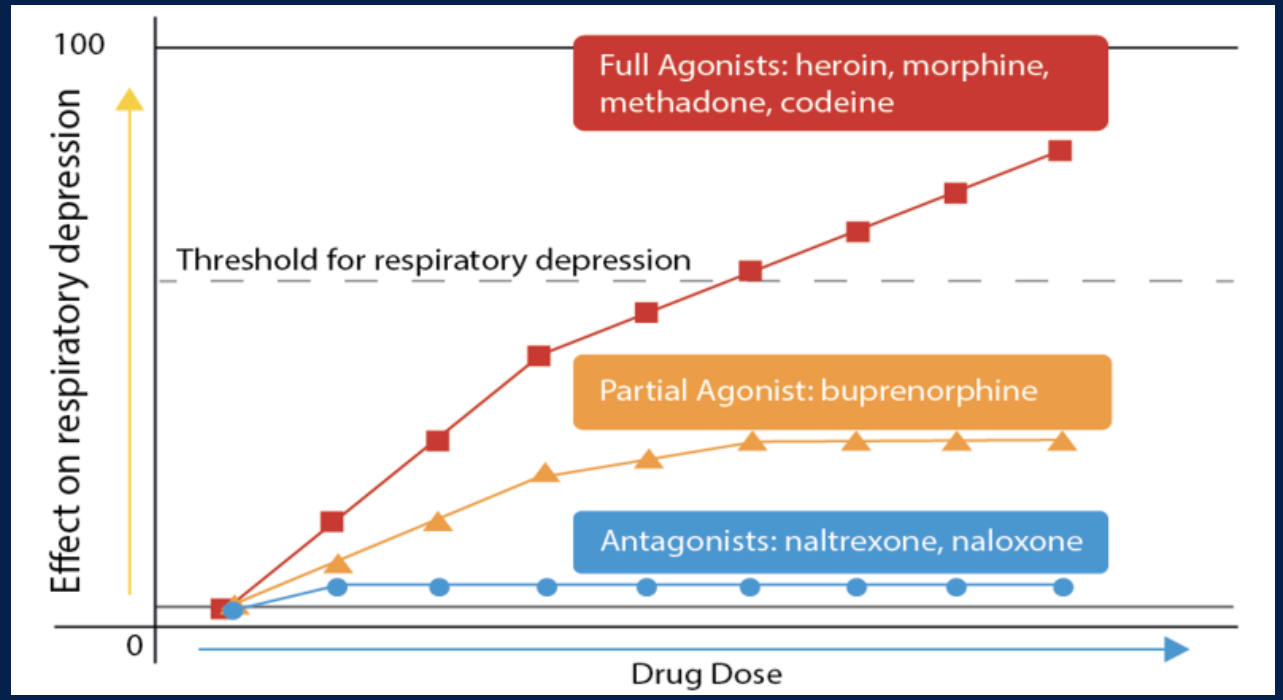
Sublingual Buprenorphine Pharmacology

- Rapid onset and long duration of action:
  - Starts to work within 30-60 minutes
  - Peak action 1-4 hours
  - Peak effect lasts 1-2 hours
  - The maximum plasma concentration : 40 minutes-3.5 hours
  - The elimination half-life 24-36 hours
- Duration of action is dose-dependent:
  - Low doses 4-8 mg: 4-12 hours
  - Moderate doses 8-12 mg: ~ 24 hours
  - Higher doses >12 mg: 2-3 days
- Antagonist at the kappa-opioid receptor
  - κ-opioid receptor contributes to the opioid's dysphoric effects
  - Possible antidepressant effects
  - Possible Antihyperalgesic effects

References: 6-10

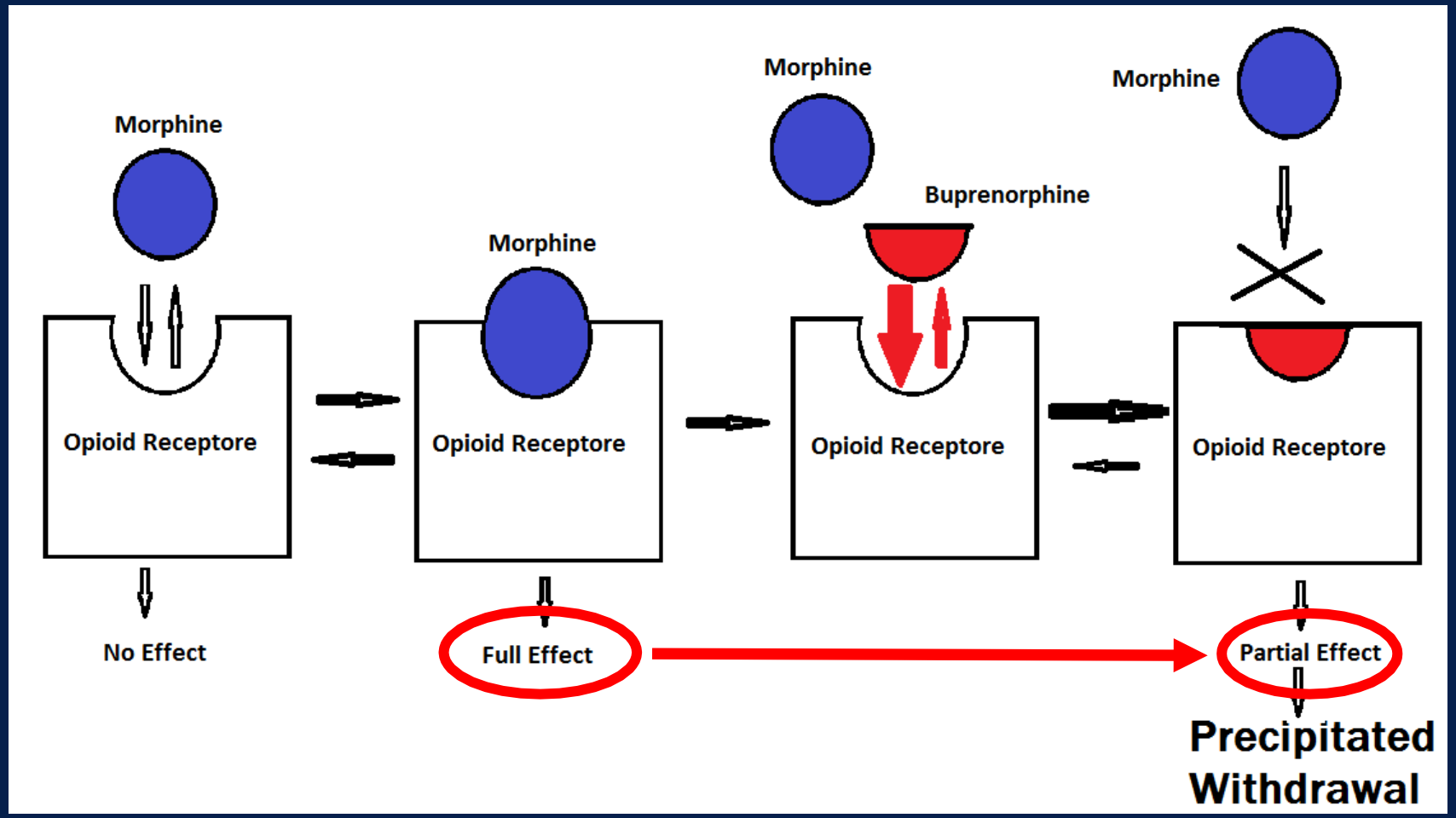
Buprenorphine

- SUBOXONE is a combination of buprenorphine and naloxone
- Semisynthetic opioid with **high affinity** for μ-opioid receptors
- Acts as a **partial agonist** at the μ-opioid receptor
- Slow rate of dissociation from the μ-opioid receptor



References: 11,12

Buprenorphine Induction Challenge



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

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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.

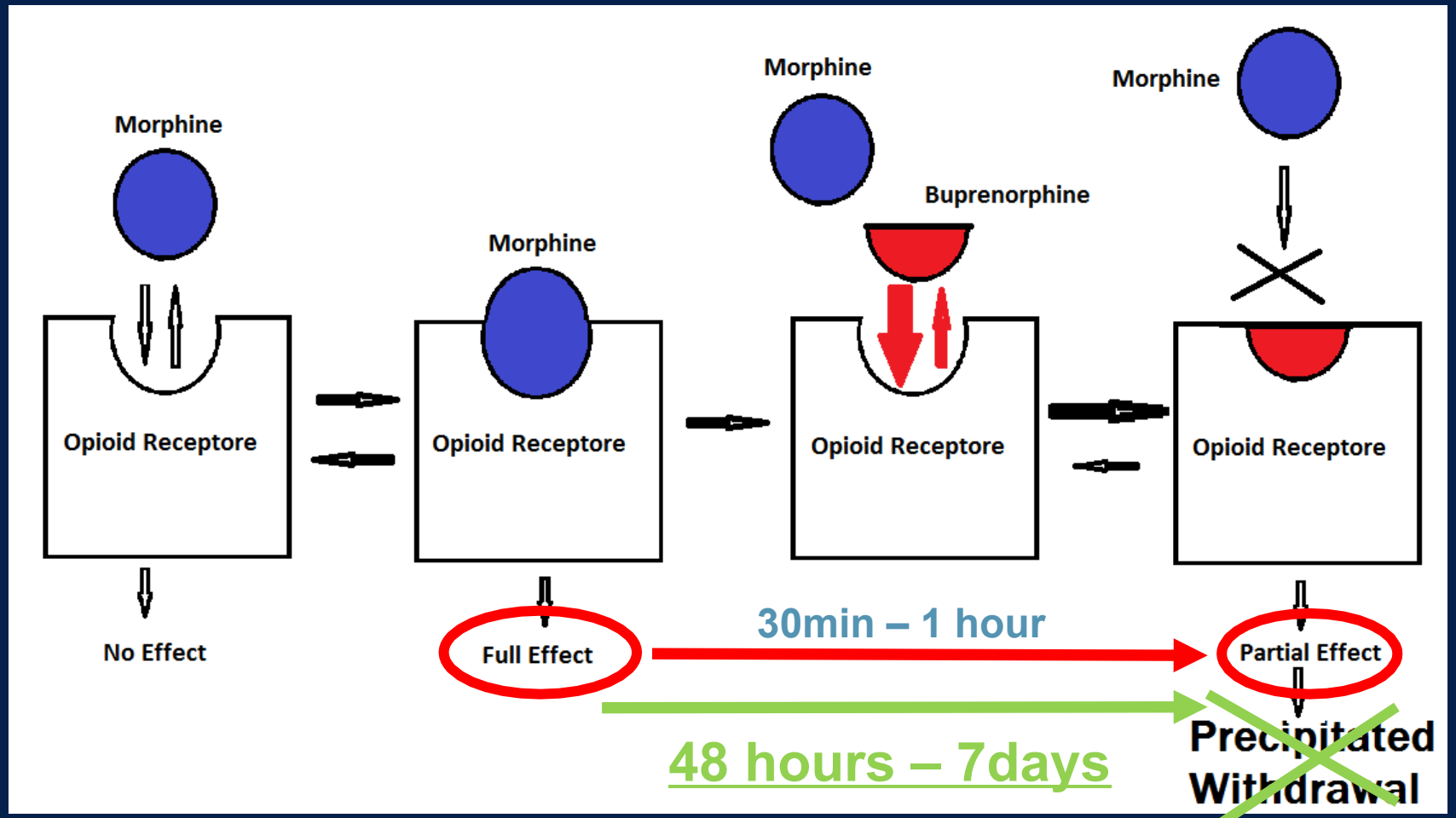
Cases: We present two cases of successful initiation of buprenorphine treatment with the Bernese method, ie, gradual induction overlapping with full agonist use. The first patient began buprenorphine with overlapping street heroin use after repeatedly experiencing relapse, withdrawal, and trauma reactivation symptoms during conventional induction. The second patient was maintained on high doses of diacetylmorphine (ie, pharmaceutical heroin) and methadone during induction. Both patients tolerated the induction procedure well and reported only mild withdrawal symptoms.

Discussion: Overlapping induction of buprenorphine maintenance treatment with full μ-opioid receptor agonist use is feasible and may be associated with better tolerability and acceptability in some patients compared to the conventional method of induction.

Keywords: subutex, suboxone, heroin, opiate, substitution

Reference 14

Buprenorphine Induction Challenge -Microdose



Buprenorphine Induction Strategies:

1. Wait for the patient to get into withdrawal
2. Induce withdrawal via naloxone and rescue via Buprenorphine (Boston)
3. Microdose-Induction (Germany - Dr. Robert Hämmig)
4. 48hrRapid Microdose-Induction (VGH)
5. Bup-XR 48hrRapid Microdose-Induction (BCCH/VGH)

References: 13-16

Case 1 CM

- 16F admitted to Vancouver Children's Hospital with after OD
- Received CPR by partner with whom she was using
- GCS 3
- Resuscitated with naloxone.
- UDS on admission
  - + fentanyl
  - + opioids
  - + amphetamines
- **PMH:**
  - HCV (untreated)
- **PPH**
  - Severe Opioid Use Disorder
  - Severe Stimulant Use Disorder ADHD
  - Trauma history
    - PTSD
    - Intergenerational trauma
    - Developmental trauma (ACE score >8)

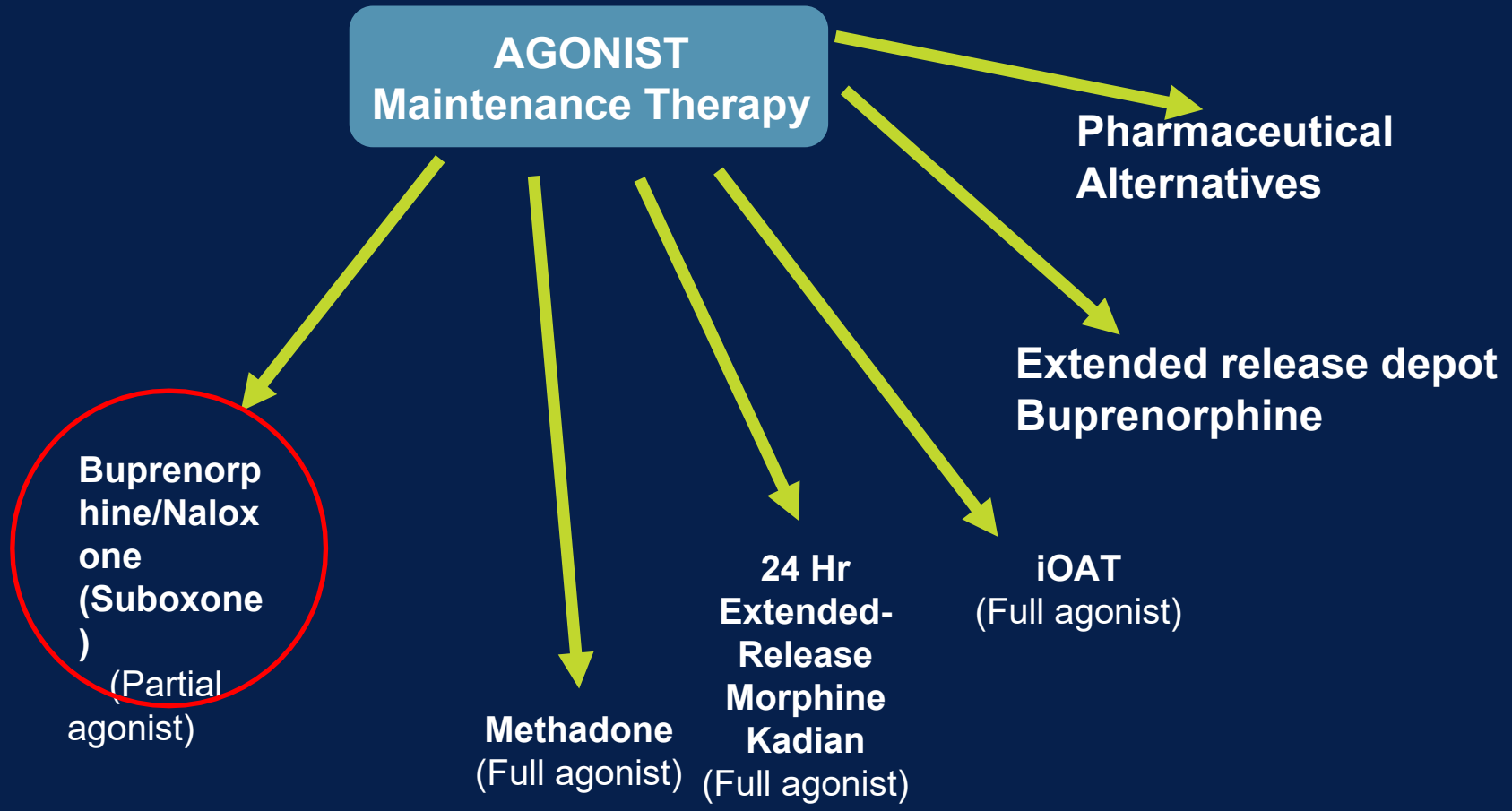
Case 1 CM: Social History

- Under voluntary care
- Protective services due to parent-child relational problems
- Living in a group home for youth with high-risk
- Spent much of her time NFA
- Attachments:
  - Mother
  - Case worker
  - BCCH

Case 1 CM: Substance Use History

- Fentanyl:
  - 0.5-1 g IV daily (last use few hours before admit)
  - 5 recent overdoses requiring naloxone
- Stimulants
  - Crystal methamphetamine
  - IV
  - Daily
- Reason For Use/Role of intoxication in pt's life:
  - "takes the pain away.." (PTSD symptoms)
- **Goal: Would like to stop fentanyl use**

Opioid Use Disorder Pharmacological Tx Options



Breakout Session #1

How would you induce the patient onto buprenorphine?
What are the pros & cons of the strategy you have chosen?
Please discuss.

5- day Outpatient Protocol

- Day 1: 0.5 mg sl BID –
  - continue opioids as usual?
  - Start full agonist
- Day 2: 1 mg sl BID
- Day 3: 2 mg sl BID
- Day 4: 4 mg sl BID
- Day 5: 12 mg sl daily - stop other opioids
- Day 6: onwards – titrate as usual

Strategies to Improve Adherence

- Partnership with local pharmacies
- Early carries
- Home delivery
- Home starts
- Blister packs
- Building support staff provide reminders and communicate issues to OAT-reach team
- Incentives for picking up meds
- Contingency Management
- Use of outreach and telehealth

Rozylo et al. Addict Sci Clin Pract (2020) 15:2
https://doi.org/10.1186/s13722-020-0177-x

Addiction Science & Clinical Practice

CASE STUDY

Open Access

Case report: Successful induction of buprenorphine/naloxone using a microdosing schedule and assertive outreach

Jennifer Rozylo[1], Keren Mitchell[1,2,3,5], Mohammadali Nikoo[1,4], S. Elise Durante[2,3], Skye P. Barbic[1,2,3,5,7,8], Daniel Lin[1,2,3,5], Steve Mathias[1,2,3,5,7] and Pouya Azar[1,2,3,5,6*]

Abstract

Background: The requirement for moderate withdrawal prior to initiation can be a barrier to buprenorphine/naloxone induction.

Case presentation: We aimed to use a microdosing regimen to initiate regular dosing of buprenorphine/naloxone in a high-risk patient with a history of failed initiations due, in part, to withdrawal symptoms. Using an assertive outreach model and a buprenorphine/naloxone microdosing schedule, we initiated treatment of an individual's opioid use disorder. There was a successful buprenorphine/naloxone microdosing induction as the team reached a therapeutic dose of buprenorphine/naloxone. Including the induction period, the medication was used consistently

Reference 17

8 days later

- Pt brought in to ED days later with Fentanyl OD Malodourous and dishevelled
- UDS + Fentanyl and methamphetamine
- Pt was not able to complete microdosing as she lost bubble pack and relapsed
- Goal remains abstinence
- Has a cellulitis and will be admitted to medicine for a 1-3 days
- Pts goal is to go back onto buprenorphine

Breakout Session #2

How would you induce the patient onto buprenorphine?
What are the pros & cons of the strategy you have chosen?
Please discuss.

The American Journal on Addictions, XX: 1–4, 2018

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12869

Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

Sukhpreet Klaire, MD, CCFP,[1] Rebecca Zivanovic, Bsc, MD,[2,3] Skye Pamela Barbic, PhD, OT,[2,4,5] Raman Sandhu, MD,[3] Nickie Mathew, MD, FRCPC,[3,6] Pouya Azar, MD, FRCPC[2,3,7]

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[2]Foundry Central Office, Vancouver, Canadian Province, Canada
[3]University of British Columbia, Vancouver, Canadian Province, Canada
[4]Department of Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, Canadian Province, Canada
[5]Centre for Health Evaluation Outcome Sciences, St. Paul's Hospital, Vancouver, Canadian Province, Canada
[6]Surrey Memorial Hospital, Surrey, Canadian Province, Canada
[7]Complex Pain and Addiction Services, Vancouver General Hospital, Vancouver, Canadian Province, Canada

Background and Objectives: Buprenorphine/naloxone has been shown to be effective in the treatment of opioid use disorder. Due to its pharmacological properties, induction can be challenging, time-consuming, and result in sudden onset of withdrawal symptoms.
Methods: Retrospective case series ($n = 2$).
Results: Two patients with opioid use disorder were successfully

line therapy.[8–11] Buprenorphine, a partial mu-opioid receptor agonist, can also be used to provide analgesia while carrying a more favorable safety profile compared to full mu-opioid agonists.[12,13] It is often combined with naloxone, a competitive opioid receptor antagonist with minimal oral and

Reference 15

Sublingual Buprenorphine Pharmacology

- Rapid onset and long duration of action:
  - Starts to work within 30-60 minutes
  - Peak action 1-4 hours
  - Peak effect lasts 1-2 hours
  - The maximum plasma concentration : 40 minutes-3.5 hours
  - The elimination half-life 24-36 hours
- Duration of action is dose-dependent:
  - Low doses 4-8 mg: 4-12 hours
  - Moderate doses 8-12 mg: ~ 24 hours
  - Higher doses >12 mg: 2-3 days
- Antagonist at the kappa-opioid receptor
  - κ-opioid receptor contributes to the opioid's dysphoric effects
  - Possible antidepressant effects
  - Possible Antihyperalgesic effects

References: 6-10

48h Induction Strategy

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

Reference 15

VA: VGH / UBCH / GFS
VC: BP / Purdy / GPC

ADDRESSOGRAPH

COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS

BUPRENORPHINE-NALOXONE (SUBOXONE) MICRODOSING INDUCTION ORDERS

Chronic Pain and Addiction Services (CPAS) - VGH

(items with check boxes must be selected to be ordered)

Time Process
RN/LPN Initi
Comments

Date: _____ **Time:** _____

Notes to Prescriber:
Refer to buprenorphine-naloxone prescribing guidelines from College of Physicians and Surgeons of BC on reverse of page 2 (page 2A).
The physician ordering buprenorphine-naloxone must call the patient's community pharmacy to discontinue any ongoing provision of opioids in the community.

LABORATORY:
- ☐ Urine drug screen (including methadone metabolites, fentanyl, oxyCODONE and opiates)
- ☐ Urine HCG for female patients (Emerg only) – notify physician before induction if HCG positive
- ☐ HCG (blood) for female patients – notify physician before induction if HCG positive

MEDICATIONS:

☐ **STANDARD MICRODOSING INDUCTION** **Start on:** _____ **(date) at** _____ **(hours)**

Day	buprenorphine dose and interval*	buprenorphine - naloxone strength to use	Quantity per dose
1	0.5 mg sublingual daily	buprenorphine 2 mg - naloxone 0.5 mg	1/4 tab
2	0.5 mg sublingual BID	buprenorphine 2 mg - naloxone 0.5 mg	1/4 tab
3	1 mg sublingual BID	buprenorphine 2 mg - naloxone 0.5 mg	1/2 tab
4	2 mg sublingual BID	buprenorphine 2 mg - naloxone 0.5 mg	1 tab
5	4 mg sublingual BID	buprenorphine 2 mg – naloxone 0.5 mg	2 tabs

Starting on Day 6, give buprenorphine-naloxone* 12 mg (1 tab) sublingual once daily ***AND*** start buprenorphine-naloxone _____ mg sublingual Q3H PRN withdrawal symptoms ***AND*** discontinue all opioids other than buprenorphine-naloxone.

☐ **RAPID MICRODOSING INDUCTION** **Start on:** _____ **(date) at** _____ **(hours)**

Doses	buprenorphine dose and interval*	buprenorphine - naloxone strength to use	Quantity per dose
1 to 8	0.5 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/4 tab
9 to 16	1 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/2 tab

Starting 3 hours after the last dose (i.e. dose number 16), give buprenorphine-naloxone* _____ mg sublingual once daily ***AND*** start buprenorphine-naloxone _____ mg sublingual Q3H PRN withdrawal symptoms ***AND*** discontinue all opioids other than buprenorphine-naloxone.

* Buprenorphine-naloxone is dosed based on buprenorphine component.

Advise patient to dissolve tablet completely under the tongue, which can take up to 10 minutes.
DO NOT swallow saliva or tablet, talk or drink during this time.

IF YOU RECEIVED THIS FACSIMILE IN ERROR, PLEASE CALL 604-875-4077 IMMEDIATELY

Vancouver CoastalHealth
VA: VGH / UBCH / GFS
VC: BP / Purdy / GPC

ADDRESSOGRAPH

COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS

BUPRENORPHINE-NALOXONE (SUBOXONE) MICRODOSING INDUCTION ORDERS

Chronic Pain and Addiction Services (CPAS) - VGH

(items with check boxes must be selected to be ordered)

Time Processed
RN/LPN Initials
Comments

Date: _____ **Time:** _____

Other as needed opioid medication for withdrawal symptoms:

Hold PRN opioid if sedated, respiratory rate below 12 per minute, or SpO_2 below 92%.
Discontinue PRN opioid: see instructions on page 1 for timing of discontinuation.

- ☐ morphine _____ mg PO or _____ mg SUBCUT Q3H PRN
- *** OR ***
- ☐ HYDROmorphone _____ mg PO or _____ mg SUBCUT Q3H PRN
- *** OR ***
- ☐ oxyCODONE _____ mg PO Q3H PRN

Adjunct medications for withdrawal management:

- ☐ dimenhyDRINATE 50 mg PO/IV Q6H PRN nausea/vomiting (maximum 400 mg per day)
- ☐ ondansetron 4 mg PO/IV Q8H PRN nausea/vomiting
- ☐ acetaminophen 325 to 650 mg PO Q4H PRN pain (maximum 4 g per 24 hour period from all sources)
- ☐ ibuprofen 200 to 400 mg PO Q6H PRN pain (maximum 2.4 g per 24 hour period)
- ☐ clonidine 0.1 mg PO Q1H PRN withdrawal symptoms (maximum 0.8 mg per day). Hold if SBP less than 100 mmHg or DBP less than 70 mmHg.
- ☐ loperamide 2 mg PO QID PRN diarrhea (Maximum 16 mg per 24 hours)
- ☐ zopiclone 3.75 mg PO QHS PRN insomnia. May repeat x 1 dose

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Pt admitted 3 days later with Fentanyl OD

- Stopped Buprenorphine second day post D/C
- Used with boy friend
- Again regretful
- IV 0.5-1 g illicit fentanyl daily (last use few hours before admit)
- At last admission, rapid micro-induction protocol used for initiation
- Did not continue as outpatient

Breakout Session #3

How would you induce the patient onto buprenorphine?
What are the pros & cons of the strategy you have chosen?
Please discuss.

Buprenorphine extended-release (BUP-XR) injection

- Patients should first undergo induction and stabilization by initiating a transmucosal buprenorphine-containing product, delivering the equivalent of 8-24 mg/day of **buprenorphine for a minimum of 7 days.**
- Following induction and stabilization, patients can be transitioned to buprenorphine extended-release injection
  - Courtesy of Dr. George Budd

Reference 18

The American Journal on Addictions, 29: 531–535, 2020

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A Case Report: Rapid Micro-Induction of Buprenorphine/Naloxone to Administer Buprenorphine Extended-Release in an Adolescent With Severe Opioid Use Disorder

Pouya Azar, MD, FRCPC,[1] James S.H. Wong, BSc,[2] Sara Jassemi, MD, FRCPC,[3] Eva Moore, MD, MSPH,[3] Dzung X. Vo, MD, FAAP, FSAHM,[3] Mohammadali Nikoo, MD,[2] Samantha Young, MD, FRCPC[4,5]

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Reference 16

BUP-XR Rapid Micro-Induction Technique

	Hydromorphone (oral)		Buprenorphine/naloxone (sublingual)[a]		BUP-XR (subcutaneous)
	Dosing	Total dose received	Dosing	Total dose received	Dose administered
Day 1	1-3 mg q3h prn	15 mg	0.5 mg q3h	3 mg	
Day 2	1-3 mg q3h prn	5 mg	1 mg q3h	7 mg	
Day 3	Discontinued		8 mg daily	8 mg	
Day 4			Discontinued		300 mg

BUP-XR = buprenorphine extended-release; prn = as needed; q __ h = every __ hours.
[a]Expressed as mg of buprenorphine component.

Reference 16

Induction Course

- Clinical Opioid Withdrawal Scale (COWS) score maximum 6 throughout induction
  - Unchanged COWS after administration of BUP-XR
- No indication of precipitated withdrawal at any time
- Discharged home a few hours after administration of BUP-XR

Course Post Dose

- No overdoses for 6 weeks post dose
- Continued to use illicit Fentanyl
- Significantly increased Methamphetamine use
- Increased psychosis
- Increases chaotic behavior
- Decreased engagement with team
- Pt refused second dose
- Now being titrated on iOAT

Conclusions

- Rapid micro-induction technique can help facilitate inpatient buprenorphine/naloxone induction within 3 days with no need to endure withdrawal
- A rapid micro-induction was used successfully to transition to BUP-XR with no precipitated withdrawal
  - May help reduce barriers for patients with difficulty adhering to buprenorphine-containing product for ≥ 7 days
- Must address underlying mental illness and social determinants of health

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Wong *et al. Addict Sci Clin Pract* (2021) 16:11
https://doi.org/10.1186/s13722-021-00220-2

Addiction Science & Clinical Practice

STUDY PROTOCOL Open Access

Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial

James S. H. Wong[1*], Mohammadali Nikoo[1], Jean N. Westenberg[1], Janet G. Suen[1], Jennifer Y. C. Wong[1], Reinhard M. Krausz[1], Christian G. Schütz[2], Marc Vogel[3], Jesse A. Sidhu[4], Jessica Moe[5,6], Shane Arishenkoff[7], Donald Griesdale[8], Nickie Mathew[4,9†] and Pouya Azar[4†]

buprenorphine micro-induction regimen. We will consider any patient or clinical outcomes defined by

Results: A 16-year-old female with active, severe opioid use disorder (OUD) and stimulant use

Thank You

Questions?

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