Induction Without Withdrawal: Buprenorphine/Naloxone Micro-Dosing

Pouya Azar, MD, FRCPC, DABAM
Nickie Mathew, MD, MSc, FRCPC, ABPN, ABPM
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.
HEROIN

FENTANYL

CARFENTANIL

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

**AGONIST Maintenance Therapy**

- **Buprenorphine/Naloxone (Suboxone)** (Partial agonist)
- **Methadone** (Full agonist)
- **24 Hr Extended-Release Morphine Kadian** (Full agonist)
- **iOAT** (Full agonist)

**Pharmaceutical Alternatives**

- **Extended release depot Buprenorphine**

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The diagram illustrates various pharmacological treatment options for opioid use disorder, categorized into agonist and antagonist maintenance therapies.
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
  - $\kappa$-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
Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

Robert Hämmig¹
Antje Kemter²
Johannes Strasser²
Ulrich von Bardeleben¹
Barbara Gugger¹
Marc Walter²
Kenneth M Dürsteler²
Marc Vogel³

¹Division of Addiction, University Psychiatric Services Bern, Bern, Switzerland; ²Division of Substance Use and Addictive Disorders, University of Basel Psychiatric Hospital, Basel, Switzerland

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, i.e., 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 (i.e., 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
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

**AGONIST Maintenance Therapy**

- **Partial agonist**
  - Buprenorphine/Naloxone (Suboxone)
- **Full agonist**
  - Methadone
  - 24 Hr Extended-Release Morphine Kadian
  - Extended release depot Buprenorphine
  - iOAT (Full agonist)

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

Jennifer Rozylo¹, Keren Mitchell¹235, Mohammadali Nikoo¹46, S. Elise Durante²3, Skye P. Barbic¹23578, Daniel Lin¹235, Steve Mathias¹2357 and Pouya Azar¹23569

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.
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
How would you induce the patient onto buprenorphine? What are the pros & cons of the strategy you have chosen? Please discuss.
Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

Sukhpreet Klare, 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, FRCPC2,3,7

1British Columbia Centre on Substance Use, Vancouver, Canadian Province, Canada
2Foundry Central Office, Vancouver, Canadian Province, Canada
3University of British Columbia, Vancouver, Canadian Province, Canada
4Department of Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, Canadian Province, Canada
5Centre for Health Evaluation Outcome Sciences, St. Paul’s Hospital, Vancouver, Canadian Province, Canada
6Surrey Memorial Hospital, Surrey, Canadian Province, Canada
7Complex 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 treated with buprenorphine/naloxone. The treatment was well-tolerated and resulted in successful detoxification.
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

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine/Naloxone*</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dosing</td>
<td>Total Daily Dose</td>
</tr>
<tr>
<td>Day 0</td>
<td>N/A</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.5 mg SL q3h</td>
<td>8 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>1 mg SL q3h</td>
<td>8 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>12 mg SL daily</td>
<td>12 mg</td>
</tr>
</tbody>
</table>

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.
### BUPRENORPHINE-NALOXONE (SUBOXONE) MICRODOSING INDUCTION ORDERS

**Chronic Pain and Addiction Services (CPAS) - VGH**

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

**LABORATORY:**
- **□** Urine drug screen (including methadone metabolites, fentanyl, oxycodone and opiates)
- **□** Urine HCO for female patients [Emigen only] - notify physician before induction if HCO positive
- **□** HCO (blood) for female patients - notify physician before induction if HCO positive

**MEDICATIONS:**

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine dose and interval*</th>
<th>Buprenorphine - naloxone strength to use</th>
<th>Quantity per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mg sublingual daily</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>1/4 tab</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mg sublingual BID</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>1/2 tab</td>
</tr>
<tr>
<td>3</td>
<td>1 mg sublingual BID</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>1 tab</td>
</tr>
<tr>
<td>4</td>
<td>2 mg sublingual BID</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>2 tabs</td>
</tr>
<tr>
<td>5</td>
<td>4 mg sublingual BID</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>2 tabs</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Dosage range</th>
<th>Buprenorphine dose and interval*</th>
<th>Buprenorphine - naloxone strength to use</th>
<th>Quantity per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>0.5 mg sublingual Q3H x 8 doses</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>1/4 tab</td>
</tr>
<tr>
<td>2 to 6</td>
<td>0.5 mg sublingual Q3H x 8 doses</td>
<td>buprenorphine 2 mg - naloxone 0.5 mg</td>
<td>1/2 tab</td>
</tr>
</tbody>
</table>

Starting 3 hours after the last dose (i.e., dosage number 15), 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 alive or tablet, talk or drink during this time.

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**Other as needed opioid medication for withdrawal symptoms:**

- Hold PRN opioid if needed, respiratory rate below 12 per minute, or SpO2 below 92%
- Discontinue PRN opioid: see instructions on page 1 for timing of discontinuation.
  - **□** morphine mg PO or **□** SUBCUT Q3H PRN
  - **□** HYDROMORPHINE mg PO or **□** SUBCUT Q3H PRN
  - **□** oxycodone mg PO Q3H PRN

**Adjunct medications for withdrawal management:**

- **□** dexamethasone 5 mg PO/QIV Q6H PRN nausea/vomiting (maximum 400 mg per day)
- **□** ondansetron 4 mg PO/IV Q6H PRN nausea/vomiting
- **□** acetaminophen 325 to 650 mg PO Q4H PRN pain (maximum 4 g per 24 hour period from all sources)
- **□** Loperamide 200 to 400 mg PO Q6H PRN diaphoresis (maximum 2 g per 24 hour period)
- **□** clonidine 0.1 mg PO Q4H PRN withdrawal symptoms (maximum 0.8 mg per day). Hold if SBP less than 100 mmHg or DBP less than 70 mmHg
- **□** zopiclone 3.75 mg PO QHS PRN insomnia. May repeat x 1 dose
Pt admitted 3 days later with Fentanyl OD

- Stopped Buprenorphine second day post D/C
- Used with boy friend
- Again regretsful
- 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.
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
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, FRCPC⁴,⁵

¹Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada
²Addictions and Concurrent Disorders Research Group, Department of Psychiatry, Institute of Mental Health, University of British Columbia, Vancouver, British Columbia, Canada
³Department of Pediatrics, Division of Adolescent Health and Medicine, B.C. Children’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada
⁴British Columbia Centre on Substance Use, British Columbia Centre for Excellence, St. Paul’s Hospital, Vancouver, British Columbia, Canada
⁵Department of Medicine, Interdepartmental Division of Addiction Medicine, St. Paul’s Hospital, Vancouver, British Columbia, Canada
# BUP-XR Rapid Micro-Induction Technique

<table>
<thead>
<tr>
<th></th>
<th>Hydromorphone (oral)</th>
<th>Buprenorphine/naloxone (sublingual)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>BUP-XR (subcutaneous)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td><strong>Total dose received</strong></td>
<td><strong>Dosing</strong></td>
<td><strong>Total dose received</strong></td>
</tr>
<tr>
<td>Day 1</td>
<td>1-3 mg q3h prn</td>
<td>15 mg</td>
<td>0.5 mg q3h</td>
</tr>
<tr>
<td>Day 2</td>
<td>1-3 mg q3h prn</td>
<td>5 mg</td>
<td>1 mg q3h</td>
</tr>
<tr>
<td>Day 3</td>
<td>Discontinued</td>
<td></td>
<td>8 mg daily</td>
</tr>
<tr>
<td>Day 4</td>
<td>Discontinued</td>
<td></td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

BUP-XR = buprenorphine extended-release; prn = as needed; q ____ h = every ____ hours.

<sup>a</sup>Expressed as mg of buprenorphine component.
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
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, Mohammadali Nikoo, Jean N. Westenberg, Janet G. Suen, Jennifer Y. C. Wong, Reinhard M. Krausz, Christian G. Schütz, Marc Vogel, Jesse A. Sidhu, Jessica Moe, Shane Arishenkoff, Donald Griesdale, Nickie Mathew and Pouya Azar

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?

pouya1844@gmail.com
nickmathew@gmail.com
james.wong@ubc.ca
References