



BRITISH COLUMBIA  
CENTRE ON  
**SUBSTANCE USE**  
*Networking researchers, educators & care providers*

## Buprenorphine/naloxone in the ED – Approach to Microinductions



CRISM



Research Institute



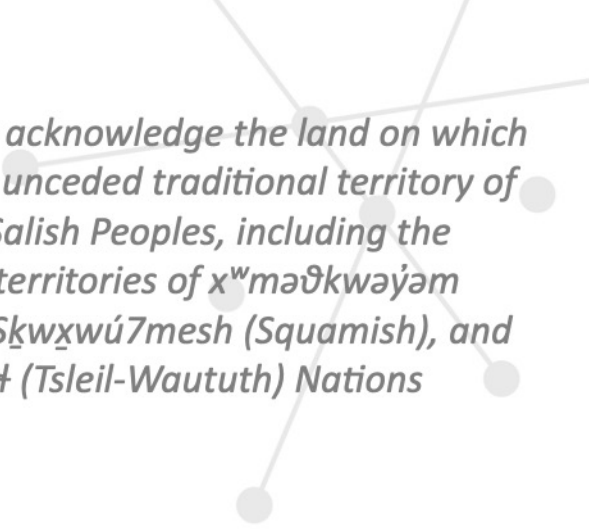
Providence



UBC



St Paul's  
FOUNDATION



*We respectfully acknowledge the land on which we work is the unceded traditional territory of the Coast Salish Peoples, including the traditional territories of x̣m̄əθkwəȳəm (Musqueam), Sḳẉx̣ẉú7mesh (Squamish), and Səḷílwətəł (Tseil-Waututh) Nations*

## Disclaimer



Some of the protocols described in this presentation have been developed in response to the ongoing opioid crisis due to fentanyl in the illicit drug supply, and may not be represented in current BCCSU Guidelines.

This includes innovative and novel approaches specific to emergency settings that are based on clinical experience. There is currently little evidence or research into the effectiveness of some of these protocols, therefore clinical judgement is advised.



## Learning Objectives

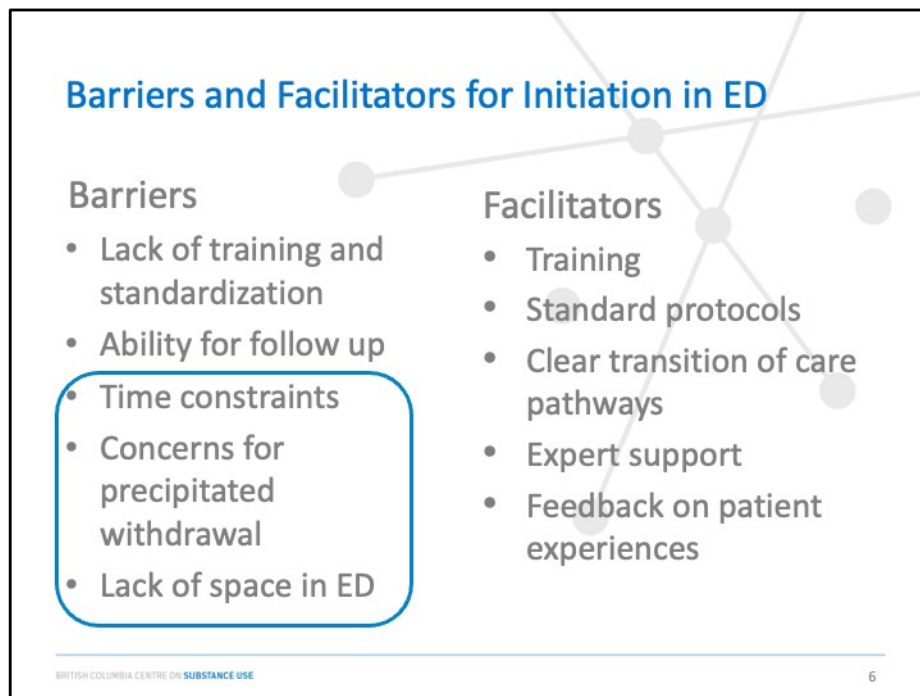
1. Describe the pharmacology of buprenorphine in how it relates to microinductions
2. Understand the evidence behind microinductions
3. Review the different approaches to microinductions
4. Outline the key steps for successful discharge

## Why Microinductions?

- Barriers associated with standard induction
  - ↑ wait for sufficient withdrawal with increased fentanyl in supply
    - 24-48 hours minimum since last fentanyl use to prevent precipitated withdrawal have been reported
  - ↑ rates of precipitated withdrawal with increased fentanyl in supply
    - Associated with higher risk of overdose and relapse
    - ↓ retention post precipitated withdrawal

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

Changes to the illicit supply have led to significant barriers for patients to be initiated onto buprenorphine via standard induction method. The increased presence of fentanyl has required patients to wait a prolonged period without opioids prior to initiation. This is to prevent the risk of precipitated withdrawal, with many reports quoting a minimum of 24-48 hours wait to avoid this. As a consequence, rates of precipitated withdrawal have increased, which is associated with a higher risk of relapse, and overdose, and decreased rates of retention onto buprenorphine.



The concern for precipitated withdrawal has also been a barrier reported by clinicians. Other barriers to standard induction for providers include the lack of physical space to monitor the patient and the time constraints around completing a standard induction in the ED, which can take several hours.



## 1. Review Buprenorphine Pharmacology

## Pharmacology of Buprenorphine

- Buprenorphine = Mu receptor partial agonist
  - High affinity, high potency
  - Low intrinsic activity
  - Slow dissociation from receptor
- For sublingual administration
  - Onset: 10-20 minutes
  - Peak: 30 min – 3 hours
  - Duration of action: dose dependent
    - <4mg: 4-12 hours
    - 8mg: 24 hours
    - 16mg: > 24 hours

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

As more is appreciated about buprenorphine's pharmacology, it's acknowledged that how it interacts with various receptors to produce a clinical effect is more nuanced than previously recognized.

Key pharmacologic principles to understand are:

- High affinity: buprenorphine will bind preferentially at the mu receptor relative to other opioids
- High potency: dose required to produce a certain effect is much lower relative to other opioids
- Low intrinsic activity: maximal effect is less than other full mu agonist, which corresponds to lower rates of respiratory depression in patients who are opioid tolerant.
- Slow dissociation: imparts a longer duration of action that is dose dependent
- Duration of action: the times noted are only estimates, and there is variability in the ranges reported in the literature.
  - This is also true for peak effect.



## Pharmacology of Buprenorphine

- Precipitated withdrawal
  - Buprenorphine shifts full agonist from Mu receptor
  - Less activity overall at receptor leads to withdrawal
  - Avoided by ensuring sufficient Mu receptors are “empty”, which is assessed by:
    - Time from last opioid use
    - Features of moderate withdrawal (COWS >12)
  - Associated with amount of buprenorphine administered

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

Buprenorphine, when taken in the presence of other full opioid agonists, will displace the full mu agonist from the receptor and create overall “less activation” of the mu receptor. This presents clinically as rapid onset of moderate-severe withdrawal.

This underpins the importance of sufficient withdrawal prior to providing typical doses of buprenorphine during a standard induction. When this criteria is met, the addition of buprenorphine will cause overall increase activation at the receptor and relief of withdrawal symptoms.

The severity and duration of precipitated withdrawal (remember slow dissociation) is related to the amount of buprenorphine administered.

COWS = clinical opiate withdrawal scale

## Pharmacology of Buprenorphine

- **Microinduction**
  - Buprenorphine taken in small increments over time in the presence of other full agonists
    - Small shifts at the Mu receptor creates a “physiologic cross taper”
  - Changes at the Mu receptor remain below the threshold to induce significant withdrawal
    - Exact threshold is unknown
  - No period of withdrawal prior to initiation required

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

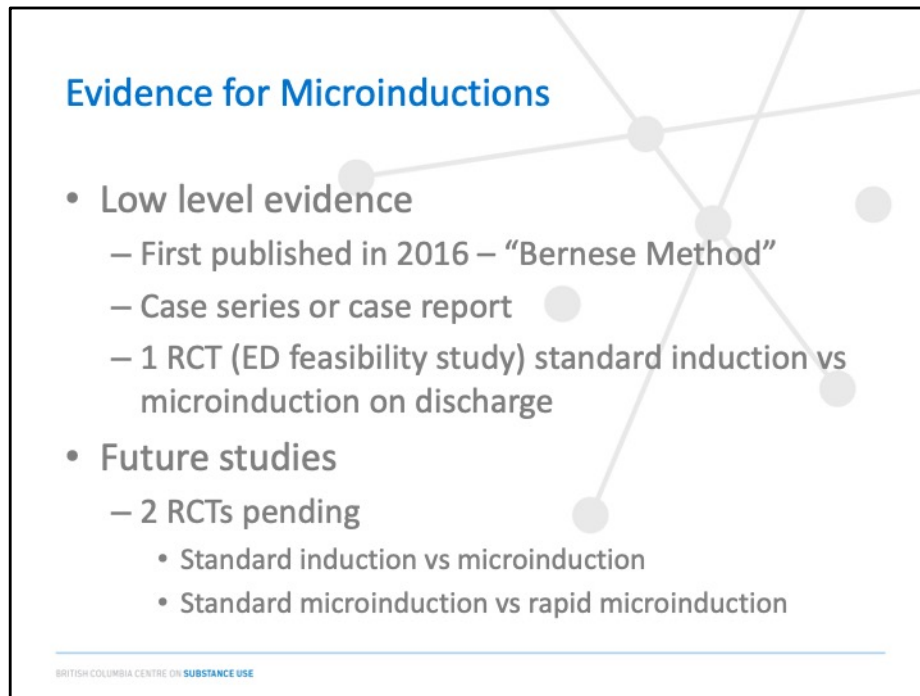
Small incremental doses of buprenorphine in the presence of full opioid agonists create shifts that stay below the threshold to induce precipitated withdrawal. This slow displacement over time is akin to a physiologic taper, with buprenorphine slowly replacing the full agonist.

The exact amount of buprenorphine that will cross the threshold for precipitated withdrawal is unknown.

Microinductions address some of the barriers cited earlier around standard inductions - there is no requirement for withdrawal or cessation of other opioid use prior to initiation.



## 2. Review of the Evidence



## Evidence for Microinductions

- Low level evidence
  - First published in 2016 – “Bernese Method”
  - Case series or case report
  - 1 RCT (ED feasibility study) standard induction vs microinduction on discharge
- Future studies
  - 2 RCTs pending
    - Standard induction vs microinduction
    - Standard microinduction vs rapid microinduction

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

First published in 2016 by Bernese et al, the theory for microinductions was based on prior studies showing low doses of IV buprenorphine (0.2mg) did not precipitate withdrawal in patients already on methadone and prior studies showing that small escalating doses of an opioid antagonist caused attenuation of withdrawal symptoms. Since the initial publication, there have been several case reports and case series highlighting different approaches in escalation of doses and within different settings (ICU, inpatient, outpatient).

The only RCT published to date was completed in the ED, comparing discharging patients with microinductions vs standard home induction.

There are two RCTs currently recruiting patients:

- The first will be comparing microinduction to standard induction on a larger scale from the ED.
- The second will be comparing a standard microinduction to a more rapid protocol in an inpatient setting.
- We will review what these protocols are later in this module.

## Evidence for Microinductions

- No consensus on approach
  - Variability in literature
  - Variability amongst providers
- 26 regimens published
  - Duration: 3-10+ days
  - Frequency: BID to q3-4h dosing
  - Starting dose: 0.3-1mg
  - Maintenance dose: 8-32mg

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

- There is a lot of variability in approaches to microinductions, both in the literature and in current clinical practice.
- This wide range of methods is based on differences in frequency of doses and rapidity of escalating dose amounts, as highlighted in the slide.
- The aim is to consolidate to a maintenance dose, which can range from 8-32mg.

## ED Specific Evidence

Received: 7 August 2020 | Revised: 27 October 2020 | Accepted: 30 October 2020  
DOI: 10.1002/emp2.12289

BRIEF RESEARCH REPORT  
Toxicology

JACEP OPEN  
WILEY

### Microdosing and standard-dosing take-home buprenorphine from the emergency department: A feasibility study

Jessica Moe MD, MSc<sup>1,2</sup> | Katherin Badke PharmD, BScPharm<sup>3</sup> | Megan Pratt MSW, RSW<sup>4</sup> | Raymond Y Cho MD, BSc<sup>5</sup> | Pouya Azar MD<sup>6,7</sup> | Heather Flemming MD<sup>1,2</sup> | K. Anne Sutherland MD, MSc<sup>1,2</sup> | Barbara Harvey MScN, JD<sup>2</sup> | Lara Gurney MSN, RN<sup>2</sup> | Julie Lockington MN, RN<sup>2</sup> | Penny Brasher PhD<sup>8</sup> | Sam Gill RN, BScN<sup>9</sup> | Emma Garrod MSN, RN<sup>10</sup> | Misty Bath MScPH, BSN<sup>11</sup> | Andy Kestler MD, MScPH<sup>1,12</sup>

- N = 46
- “To go” kits with usual supportive treatment
  - 6 day Microinduction vs 3 day standard take-home dosing
- Retained on any opioid agonist therapy (OAT) at 30 days: 32% vs 23.8%
  - Remained on buprenorphine: 62.5% vs 40%

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

14

The only RCT published to date comparing microinductions to standard inductions was this feasibility study from the ED.

When comparing to go kits dispensed from the ED on patient discharge, the microinduction arm showed higher retention rates on buprenorphine at 30 days.

## Study Protocol For Microinduction (6 day)

Day	Dose	Number of tablets per dose (buprenorphine-naloxone 2 mg-0.5 mg tablet)
1	Buprenorphine 0.5 mg-naloxone 0.125 mg SL BID	One-quarter tablet
2	Buprenorphine 1 mg-naloxone 0.25 mg SL BID	One-half tablet
3	Buprenorphine 2 mg-naloxone 0.5 mg SL BID	1 tablet
4	Buprenorphine 3 mg-naloxone 0.75 mg SL BID	One and a half tablet
5	Buprenorphine 4 mg-naloxone 1 mg SL BID	2 tablets
6	Buprenorphine 12 mg-naloxone 3 mg SL Daily	6 tablets

- Based on most reported protocol in literature

Their microinduction protocol was based on the most common protocol published in the literature.

**ED Specific Evidence**

*ClinicalTrials.gov* Find Studies ▾ About Studies ▾ Submit Studies ▾

Home > Search Results > Study Record Detail

Information provided by (Responsible Party):  
Jessica Moe, University of British Columbia

**Evaluating Buprenorphine/Naloxone Microdosing vs. Standard Dosing in Emergency Departments**

- RCT – 5 day standard home induction vs 5 day microinduction protocol from ED
  - Kits dispensed from ED
- Outcomes - completion of induction + retention on OAT

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE 16

A larger scale study is currently being undertaken looking at this question over multiple ED sites.



## Study Protocol (5 day Induction)

### Standard Induction

Day 1: Buprenorphine 2 mg-naloxone 0.5 mg SL q1h prn to a maximum of 6 tablets in the first 24 hours (1 tablet),

Day 2: Buprenorphine 12 mg-naloxone 3 mg SL once daily (6 tablets),

Day 3: Buprenorphine 16 mg-naloxone 3 mg SL once daily (8 tablets),

Day 4: Buprenorphine 16 mg-naloxone 3 mg SL once daily (8 tablets),

Day 5: Buprenorphine 16 mg-naloxone 3 mg SL once daily (8 tablets).

### Microinduction

Day 1: Buprenorphine 0.5 mg-naloxone 0.125 mg SL\* QID\*\* (One quarter tablet),

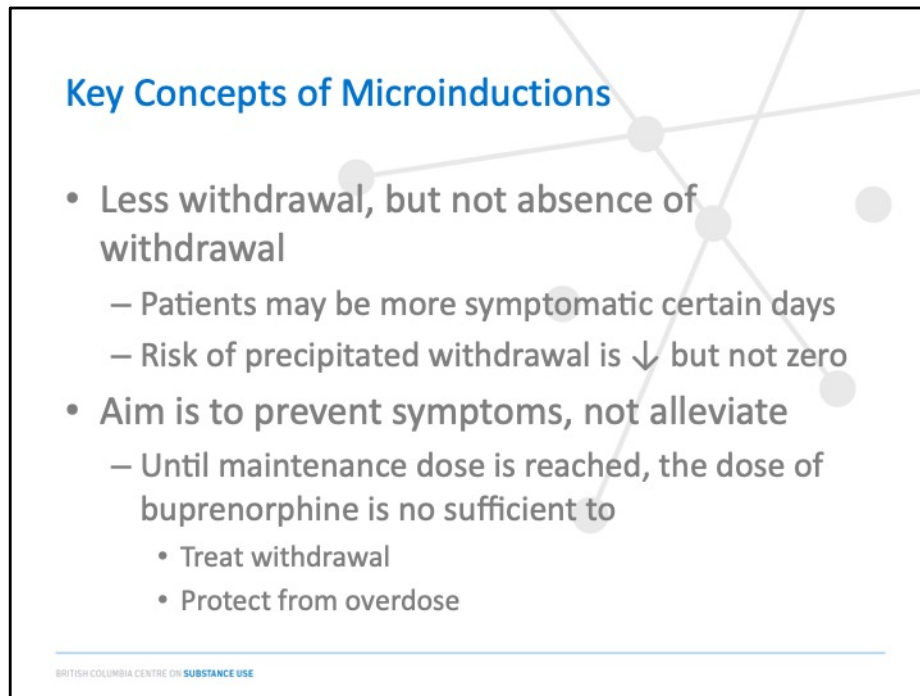
Day 2: Buprenorphine 1 mg-naloxone 0.25 mg SL QID (One half tablet),

Day 3: Buprenorphine 2 mg-naloxone 0.5 mg SL QID (1 tablet),

Day 4: Buprenorphine 3 mg-naloxone 0.75 mg SL QID (1.5 tablets)

Day 5: Buprenorphine 16 mg-naloxone 4 mg SL once daily (8 tablets).

This study will be comparing a microinduction protocol that is slightly faster (QID) to a standard 5 day home induction.



### Key Concepts of Microinductions

- Less withdrawal, but not absence of withdrawal
  - Patients may be more symptomatic certain days
  - Risk of precipitated withdrawal is ↓ but not zero
- Aim is to prevent symptoms, not alleviate
  - Until maintenance dose is reached, the dose of buprenorphine is no sufficient to
    - Treat withdrawal
    - Protect from overdose

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

There are key features of microinductions to understand in order to best prepare your patient.

#### Patients will feel less withdrawal, but not complete absence of withdrawal symptoms

- Small shifts happen at the receptor between buprenorphine and other full opioid agonist, and may translate clinically to minor withdrawal symptoms.
  - Depending on the protocol, patients may experience symptoms more commonly and to a greater degree on certain days.
- Although the risk of precipitated withdrawal is significantly reduced, the risk is not zero.
  - We do not know the exact threshold at which buprenorphine causes precipitated withdrawal in the presence other opioids, which likely is influenced by individual patient factors.

#### The aim of microinductions is to prevent risk of precipitated withdrawal, not alleviate withdrawal

- Doses of buprenorphine aim to prevent (precipitated) withdrawal symptoms but are insufficient to relieve withdrawal symptoms.
- Typically, maintenance dose of at least 8mg once daily (not split) are required to

treat withdrawal and protect from overdose. Patients generally require doses of 12-16mg or more to achieve these goals.

## Key Concepts of Microinductions

- Ensure to discuss strategies to keep the patient safe and address symptoms of withdrawal
  - Treat withdrawal symptoms with full agonist opioid
    - Prescribed through OAT provider: methadone, SROM, risk mitigation
    - Ongoing use of illicit opioids (i.e. fentanyl)
  - If unable to prescribe full agonist or not feasible for patient
    - Can provide other non opioid medications for supportive management
    - Discuss ongoing use of fentanyl to treat withdrawal and review harm reduction strategies

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

To support patients through their microinduction, the following strategies can be used to treat withdrawal symptoms and/or promote safety.

To treat withdrawal and reduce use of illicit opioid, prescribers may provide concurrent OAT (methadone, SROM).

In the context of COVID, risk mitigation prescribing has been another tool available to patients and providers, where daily dispense hydromorphone tabs (typically 8mg in strength) can be prescribed to reduce the use of toxic supply. See below for more information.

This is often not available or feasible to ED physicians:

- They are not trained to provide full agonist OAT (methadone, SROM).
- They are not following up with patients in the community to reassess benefits and risk of risk mitigation prescribing.
- There is limited time to provide informed consent around risk, benefits and expectations with risk mitigation prescribing.

ED providers can support patients by

- Explaining that patients can continue to use illicit opioids, including fentanyl, to

treat withdrawal until they reach a maintenance dose of buprenorphine (like the case published by Bernese et al).

- Review harm reduction and safer use of illicit opioids (see module on harm reduction)
- Can consider prescribing medications that would be used for symptomatic management during a standard induction, such as clonidine, acetaminophen, NSAIDs etc.

SROM = slow-release oral morphine or Kadian

For more information on risk mitigation: <https://www.bccsu.ca/wp-content/uploads/2020/04/Risk-Mitigation-in-the-Context-of-Dual-Public-Health-Emergencies-v1.5.pdf>

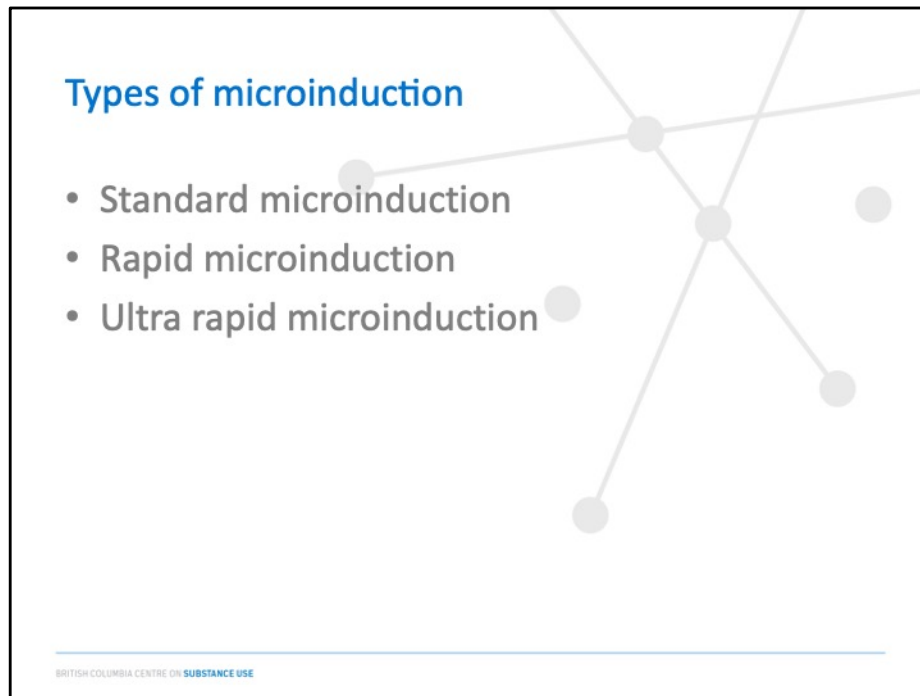
## Key Concepts of Microinductions

- Microinductions are time intensive and take work from your patients
  - Keep this in mind when choosing a protocol
  - Medication compliance: ↓ >50% with frequencies of TID or more in any prescription
- Avoid doses lower than 0.5mg
  - Difficult to cut tabs smaller than 1/4

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

Microinductions require patients to keep track of doses, while treating their withdrawal – this can be a time intensive process for many. Although no protocols have been compared head-to-head, keep in the mind your patient's setting and stability when choosing the frequency of dose administration. In outpatient settings, more frequent dosing may lead to decrease patient compliance, in particular doses that are prescribed TID and beyond. *(Patient compliance with medication is reduced by >50% when dosing frequency is TID or greater in the community)*

Some protocols start at ever lower doses (0.25mg). However, this is not practical in most settings – 2mg tabs cannot be cut consistently when cut smaller than in ¼.



Protocols vary along a spectrum of duration and rapidity of dose escalation/frequency.

For simplicity, we will review 3 broad categories, with recognition that there is significant overlap between each.

## “Standard” Microinduction

- Doses frequency = no doses overlap with duration of action
  - Duration of action of doses 4mg or below: 4-12 hours
- Typically BID dosing for simplicity
  - Bernese: q12h
  - More feasible for patients: BID with 6-8 hours between doses
- Duration: 7 days

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

Dosing frequency for a “standard microinduction” is based on duration of action of buprenorphine at doses below 4mg and avoiding overlap.

The Bernese method was grounded on the longer reported time (12 hours), which lends itself well to BID dosing.

Pragmatically, patients can safely take doses 6-8 hours apart, which is approximately the average of the reported range.



## Protocol Example 1

Day	Dose
Day 1	0.5mg OD
Day 2	0.5mg BID
Day 3	1mg BID
Day 4	2mg BID
Day 5	4mg BID
Day 6	8mg OD
Day 7	12mg OD

- First protocol used after publication of Bernese method
- Disadvantage
  - Day 1 0.5mg once daily not required
    - No advantage to reduce precipitated withdrawal (duration of action <12 hours)
    - Delayed consolidation to maintenance dose

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

This protocol was more common initially after the Bernese method was published. It was noted in clinical application that the first single dose of 0.5mg was not required to prevent precipitated withdrawal but delayed ultimately consolidation to maintenance dose.

## Protocol Example 2

Day	Dose
Day 1	0.5mg BID
Day 2	1mg BID
Day 3	2mg BID
Day 4	3mg BID
Day 5	4mg BID
Day 6	12mg OD
Day 7	16mg OD

### Advantage

- Remove first day of OD 0.5mg and added 16mg (more common maintenance dose)
  - Consider stopping at 12mg for patients with lower tolerance
- Increase from 2mg BID (4mg) to 4mg BID(8mg) could cause symptoms
  - Addition of 1 day of 3mg BID

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

This second iteration was adjusted to reflect this clinical practice. It was also noted that the jump from 2mg BID (4mg) to 4mg BID(8mg) from the previous protocol was often too quick for patients and lead to increased symptoms. An intermediary day was added with 3mg BID.

More commonly, patients will consolidate to 16mg or more. With patients who exhibit lower tolerance (for example only prescription opioids), you could consider stopping at day 6.

## Protocol Example 2

Day	Dose
Day 1	0.5mg BID
Day 2	1mg BID
Day 3	2mg BID
Day 4	3mg BID
Day 5	4mg BID
Day 6	12mg OD
Day 7	16mg OD

### Disadvantage

- Binding of buprenorphine to mu receptor relative to dose  $\neq$  linear
  - Larger change near doses of 8mg daily
  - More symptoms on first day with 8mg total daily dose – 4mg BID
- First day of consolidated dose = can experience more symptoms
  - Consolidation of dose follows day 5 (4mg BID)

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

There are two days where patients may feel more symptomatic during this protocol

1. Anecdotally, patients feel more withdrawal symptoms during day 5 of the last 2 protocol, where you can see the total daily dose equals 8mg (4mg BID).
  - Binding to the mu receptor by buprenorphine is not linear. There are more significant changes when doses near 8mg total daily.
2. The second is when doses are first consolidated to once daily. You can see that this occurs on day 6, the day following when the patient receives a total daily dose of 8mg.

### Protocol Example 3 – Suggested Protocol

Day	Dose
Day 1	0.5mg BID
Day 2	1mg BID
Day 3	2mg BID
Day 4	3mg BID
Day 5	4mg BID
Day 6	6mg BID
Day 7	8mg BID

#### Advantage

- Maintenance of split dose
  - Reduce potential sequential “symptomatic days”
  - Ease for patient administration in outpatient setting and discharge instructions: consistent frequency

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

This third example addresses prior concerns by continuing split (BID) dosing throughout.

Consolidation to 16mg occurs after completion of the microinduction (day 8).

It also offers the advantage of consistent dosing for ease of patient instruction and compliance.

## "Standard" Microinduction

- Frequently prescribed as "carry doses" (no witnessed doses in the pharmacy) - blister pack medication for ease of administration
- Consider providing first test dose in the ED to ensure proper administration
- Review key days where symptoms may be more pronounced
  - First day receives total 8mg
  - First day of consolidated dose

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

- Frequently microinductions are prescribed as carry doses.
  - Ensure to write "blister pack" on the prescription for ease of administration. Otherwise, all the buprenorphine tabs are dispensed in a single prescription bottle.
  - Many patients may not be familiar with the administration of buprenorphine or may need a reminder. Consider providing a test dose of 0.5mg in the ED to review this.
- Provide anticipatory guidance to your patients around key days where withdrawal may be more prominent – this allows your patient to navigate the microinduction with more ease.

## “Standard” Microinduction – ED Provider Approach

- Address withdrawal symptoms during microinduction
  - Review can continue to use opioids (fentanyl, heroin, hydromorphone) during microinduction
    - Treat withdrawal and cravings until dose is consolidated to once daily maintenance dose
    - Harm reduction practices given risk of overdose
  - Prescribe medications for symptomatic treatment such as:
    - Acetaminophen, NSAIDs, clonidine

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

In addition to the guidance presented in previous slides, other ways to support your patient include reviewing how they can continue to treat their withdrawal symptoms safely during the microinduction.

## ED Case Example

32 year old female presents to ED for leg cellulitis. She's experienced several overdoses in the last month while using ½ g of fentanyl/day and is hoping to start suboxone.

Prior attempts have been unsuccessful – she is unable to go through a sufficient period of withdrawal.

How does this look practically on shift? Let's look at a case example.

## ED Case Example – Discharged Patient

- Rx for BID dosing x 7 days blister packed
- Discharge instruction sheet given and reviewed verbally with patient
  - Timed with antibiotics
  - Informed can continue using fentanyl for withdrawal during microinduction
- Provided with acetaminophen, ibuprofen, clonidine for symptom relief
- Provided with THN kit

Day 1	0.5mg BID
Day 2	1mg BID
Day 3	2mg BID
Day 4	3mg BID
Day 5	4mg BID
Day 6	6mg BID
Day 7	8mg BID



## “Standard” Microinduction – OAT Provider Approach

- Strategies used by addiction specialist
  - Address initial withdrawal symptoms and help reduce illicit opioid use by concurrently prescribing the following until day 5-7:
    - Full agonist OAT (methadone, SROM)
    - +/- Risk mitigation interventions, such as hydromorphone tabs daily dispense
  - Buprenorphine/naloxone may be prescribed as
    - Carries in blister pack
    - Daily dispensed with their full agonist OAT and/or risk mitigation
  - May extend microinductions for patients prescribed high doses of full agonist OAT already
- Can be considered in ERP with experience with OAT and an agreement with a designated follow up clinic

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

### Reduce withdrawal and use of illicit opioid

Some strategies used by community OAT providers or addiction specialist to reduce the burden of withdrawal symptoms and reduce use of illicit opioids include concurrent prescription of:

- OAT: this includes continuation or initiation of either methadone or SROM
- Risk mitigation prescribing (hydromorphone 8mg tabs daily dispense) has become an option to reduce the use of the toxic supply and help promote self isolation in the context of COVID. Ideally, this should be prescribed by the same provider or prescribing group (shared care clinic) for monitoring, including reassessment of benefit and potential harms.
- Please refer to the modules reviewing other full agonist OAT (methadone and SROM) and risk mitigation for more details.

### Prescribing buprenorphine microinduction

- Given its favorable safety profile, buprenorphine can be prescribed as carry doses. This can be done even with concurrent OAT prescription which requires patients to have daily witnessed ingestions in pharmacies.
  - It should ideally be via blister pack for ease of administration.
- Otherwise, doses can be daily dispensed with their OAT (but no witnessed doses

required) for patients who prefer more structure.

**For patients already on OAT**

- Microinductions may be extended for patients already prescribed higher doses of OAT. There will be an example in the following slides.
- There is no definition for what is considered higher doses of OAT, but this may be considered for patients on doses of methadone >100mg or SROM>1000mg.

## Example of Standard Microinduction with concurrent OAT initiation and Risk Mitigation

Day	Buprenorphine/Naloxone	Methadone	Hydromorphone risk mitigation
1	0.5mg BID	30mg po daily (Daily witnessed ingestion - DWI)	8mg tabs – daily dispense 6 tabs 1-2 tabs po q3h PRN for withdrawal
2	1mg BID	30mg po daily (DWI)	6 tabs
3	2mg BID	30mg po daily (DWI)	6 tabs
4	3mg BID	30mg po daily (DWI)	6 tabs
5	4mg BID	30mg po daily (DWI)	6 tabs
6	6mg BID	30mg po daily (DWI)	6 tabs
7	8mg BID	30mg po daily (DWI)	6 tabs
8	Reassess in clinic – Consolidate to 16mg OD	Stopped	

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

DWI – Daily witnessed ingestion

## Example of Prolonged Microinduction with High Dose OAT

Day	Buprenorphine/Naloxone	Methadone
1	0.5mg BID	120mg po daily (DWI)
2	1mg BID	120mg po daily (DWI)
3	2mg BID	120mg po daily (DWI)
4	3mg BID	120mg po daily (DWI)
5	4mg BID	120mg po daily (DWI)
6	6mg BID	120mg po daily (DWI)
7	8mg BID	120mg po daily (DWI)
8	10mg BID	120mg po daily (DWI)
9	12mg BID	120mg po daily (DWI)
10	24mg OD	Stopped

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

This is a case example where the patient would present already on a maintenance dose of methadone (120mg).

## Rapid Microinduction

- Dose frequency – QID
  - 4 hours between doses
  - Based on peak effect
  - Based on shorter duration of action at lower doses
  - Allows to reach steady state (4 doses/day)
- Duration: 4-5 days
  - More frequent dosing will allow patient to reach a therapeutic dose more quickly
- Consider in patients with
  - More stability
  - Time constraints

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

A rapid microinduction structures its frequency based on the shorter range of duration of action (4 hours) and on peak effect of buprenorphine (3 hours for the longest estimate).

QID dosing (with 3-4 hours between doses) allows for steady state to be established for each dose (4 doses per day), and for patients to reach a therapeutic dose more quickly (4-5 days).

This approach is ideal for patient who have more time constraints (shorter time till consolidation) and have more stability (due to more frequent dosing).

## Protocol Example 1

Day	Dose
Day 1	0.5mg QID
Day 2	1mg QID
Day 3	2mg QID
Day 4	8mg OD

- Consider in patients with lower opioid tolerance

This protocol consolidates to 8mg. This can be considered for patients with lower opioid tolerance, given most will require dose of 12-16mg at minimum to reach stability.

## Protocol Example 2

Day	Dose
Day 1	0.5mg QID
Day 2	1mg QID
Day 3	2mg QID
Day 4	3mg QID
Day 5	12-16mg OD

- Suggested protocol
  - Consider in patients with high opioid tolerance
  - Allows to reach higher maintenance dose

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

This approach aims to consolidate to more typical starting maintenance doses (12-16mg).

Day 5 can include consolidation to 12mg (total daily dose from day 4), but patients have tolerated consolidation to 16mg in clinical experience.

## Rapid Microinduction

- More flexibility with missed doses
  - Can miss 1 dose per day and no adjustment likely required
    - 3 doses = ~87% steady state
- Ensure prescribed as blister pack
- Strategies by addiction specialist like approach with standard microinduction
  - Concurrent OAT and/or risk mitigation
  - Prescribed until day 4-5 (consolidation day)

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

The rapid microinduction allows some flexibility with missed doses relative to the standard induction.

If the patient receives 3 doses, they are likely at sufficient steady state to proceed (estimated 87%).

Given the higher technical requirements for the patient, blister pack is always recommended to facilitate completion.

Strategies to treat withdrawal during these rapid microinductions are like standard induction – please see previous slide outlining this in more detail.



## Ultra-Rapid Microinduction

- Dose frequency: q3-4h (24 hour administration)
  - Dose based on peak effect (1-3 hours)
  - Consider q4h in ED for more flexibility
- Duration: 2-3 days
- Consider for patients
  - Significant time constraints
  - Held overnight in the ED
  - Ability or willingness to stay up overnight
- ED setting limitations
  - Nursing workload
  - Ability to administer medications q3-4h

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

The “ultra-rapid” microinduction takes the same principles as the rapid microinduction, but increases the frequency to q3-4h with continuous administration over 24 hours. Maintenance dose is reached by 2-3 days.

This should be considered in patients who have (1) significant time constraints and (2) are willing to stay awake overnight.

In the ED, this could be an intervention for patients who are held overnight for reassessment. Although not specific to microinduction, patients who are held overnight for monitoring and reassessment in clinical decision units have higher retention rates on buprenorphine/naloxone.

Some limitations in the ED include:

- Ability to administer medications every 3-4 hours depending on the patient’s location. Consider ordering q4h to allow more flexibility for delayed or early doses.
- Additional workload to nurses – depending on other department demands, this frequency may not be feasible.

## Protocol Example 1

Day	Dose
1	0.5mg q3h x 8
2	1mg q3h x 8
3	8mg OD

Most feasible in ED

### Advantage

- Consistent dosing each day
- Allows for missed doses

### Disadvantage

- Consolidation at lower dose

This protocol is the most feasible in the ED, given the consistent dosing over 24 hours allows more flexibility for missed doses, and dose delays.

## Protocol Example 2

Day	Dose
1	0.5mg q3-4h x 4 doses 1mg q3-4h x 4 doses
2	2mg q3-4h x 4 doses 3mg q3-4h x 4 doses
3	16mg OD

### Advantage

- Reach higher maintenance dose
- Reach steady state (4 doses) before proceeding to next dose

### Disadvantage

- Possible increased risk of error given frequent change in dose
- Less flexibility for missed doses

## ED Case Example

32 year old female presents to ED for leg cellulitis. She's experienced several overdoses in the last month while using ½ g of fentanyl/day and is hoping to start suboxone.

Prior attempts have been unsuccessful – she is unable to go through a sufficient period of withdrawal.

Similar to our case from earlier, but this time our patient is being held overnight for further monitoring.

## Scenario 2 – Overnight in ED

- Held overnight to be monitored for response to antibiotics
- Order “rapid microinduction” approach:
  - 0.5 mg SL q3h until seen by addiction specialist or reassessed in AM

Dunkley 2019

## Ultra-Rapid Microinduction

- If supervised within ED
  - Order PRN IR opioids for withdrawal: hydromorphone is recommended due to its higher affinity
  - Consider q4h dosing of buprenorphine rather than q3h
    - Allows for more flexibility for any delays
- If discharged home
  - Consider blister pack:
    - Each row is assigned one dose strength for protocol example 2
  - Provide medications symptomatic management within your comfort

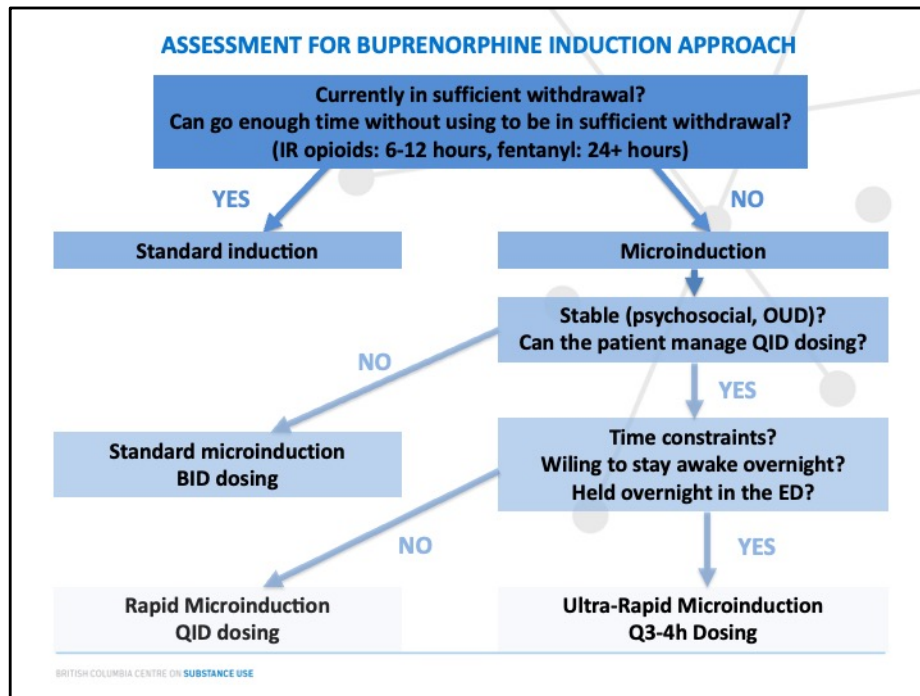
BRITISH COLUMBIA CENTRE ON SUBSTANCE USE

### In the ED (acute care)

- Most ultra-rapid microinductions are completed in an acute care setting. It can be difficult for patients to manage without support.
- Ensure to order IR opioids as needed for withdrawal during their stay.
  - Hydromorphone is the ideal choice given its higher affinity for the MU receptor relative to morphine – an example would be hydromorphone 4-6mg po q2h PRN for withdrawal.
- Ensure the patient is situated in an area that can accommodate this regimen. An alternative would be prolonging to q4h to allow more flexibility with delays.

### Outpatient setting (discharged home)

- There are exceptional cases where patients choose to complete this as an outpatient – motivations tend to be extreme time constraints.
- if using the second protocol, consider blister packing with each “row” being 1 dose strength.
  - If using the first protocol, this is not required.
- Provide the patient with all the tools necessarily to treat their withdrawal in the interim: either reviewing safer use of their illicit supply or prescribing symptomatic management (clonidine).



Here is an algorithm that can help guide your choice of protocol.

1. Always assess whether the patient can be initiated via standard induction. This will provide the fastest pathway to a stable dose.
2. If the wait time is a barrier, microinductions is your alternative.
3. To decide between a standard and a rapid microinduction, assess the patient's stability outside the hospital and ask the patient whether QID dosing is feasible for them.
4. You can consider a rapid ultra microinduction in patients who are being held overnight in the ED or have time constraints.
  1. Provide informed consent by letting the patient know they will wake up throughout the night for doses.

## Transition of Care

- Clear pathway, and low barrier referrals for community follow up
- Discharge instructions – patient dissatisfaction linked with decreased likelihood of filling prescription
  - Written instructions/information sheet
  - Patient-centered language = better understanding (e.g. number of pills to take, times, pictures)
  - Clear messaging with no medical jargon and appropriate literacy
  - Review instructions verbally
- Outreach to support follow up
- Consider follow up by phone post discharge for check in



## Transition of Care

- Discharge instructions
  - Review protocol with patient
  - Anticipatory guidance on symptoms:
    - Some withdrawal is anticipated
      - Certain days will be more pronounced (i.e. 4mg BID or consolidation of dose)
    - Severe withdrawal within 15-30 min of dose is not expected and indicative of precipitated withdrawal
  - Precipitated withdrawal risk is reduced but not zero
    - Missed doses increases the risk of precipitated withdrawal
    - Present to care to be reassessed if missed doses or significant withdrawal symptoms

## Transition of Care

- Discharge instructions (continued)
  - Doses will be insufficient to treat withdrawal or protect from overdoses
    - Review harm reduction and safer use
    - Provide medications for symptomatic management (i.e., clonidine, acetaminophen etc.)
    - Consider urgent referral for possible full agonist and/or risk mitigation initiation

Risk mitigation can be considered if the ED provider has an understanding of the current guidelines, can explain the intent of the intervention to the patient and has an agreement with a follow up clinic to take on continuation of risk mitigation prescribing.

## Limitations and Differences from Other Settings

- Lack of clear protocol – 26 regimens reported in the literature with heterogenous settings and patient characteristics
- Time for discharge instructions (average duration 76 seconds)
- Lack of full agonist prescribing capabilities or comfort by ERP

Moe 2020, Engel 2019

## References

1. Spadaro A, Sarker A, Hogg-Bremer W, Love JS, O'Donnell N, Nelson LS, et al. Reddit discussions about buprenorphine associated precipitated withdrawal in the era of fentanyl. n.d.;
2. Randhawa PA, Brar R, Nolan S. Buprenorphine–naloxone “microdosing”: an alternative induction approach for the treatment of opioid use disorder in the wake of North America’s increasingly potent illicit drug market. *CMAJ*. 2020;192(3):E73–E73.
3. Whitley SD, Sohler NL, Kunins HV, Giovanniello A, Li X, Sacajiu G, et al. Factors associated with complicated buprenorphine inductions. *J Subst Abuse Treat*. 2010;39(1):51–7.
4. Antoine D, Huhn AS, Strain EC, Turner G, Jardot J, Hammond AS, et al. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. *Am J Addict*. 2021;30(1):83–7.
5. Dong KA, Lavergne KJ, Salvalaggio G, Weber SM, Xue CJ, Kestler A, et al. Emergency physician perspectives on initiating buprenorphine/naloxone in the emergency department: A qualitative study. *J Am Coll Emerg Physicians Open*. 2021;2(2):e12409.
6. Lowenstein M, Kilaru A, Perrone J, Hemmons J, Abdel-Rahman D, Meisel ZF, et al. Barriers and facilitators for emergency department initiation of buprenorphine: A physician survey. *Am J Emerg Medicine*. 2019;37(9):1787–90.
7. Hawk KF, D’Onofrio G, Chawarski MC, O’Connor PG, Cowan E, Lyons MS, et al. Barriers and Facilitators to Clinician Readiness to Provide Emergency Department–Initiated Buprenorphine. *Jama Netw Open*. 2020;3(5):e204561.
8. Wiercigroch D, Hoyeck P, Sheikh H, Hulme J. A qualitative examination of the current management of opioid use disorder and barriers to prescribing buprenorphine in a Canadian emergency department. *Bmc Emerg Medicine*. 2021;21(1):48.
9. Kim HS, Samuels EA. Overcoming Barriers to Prescribing Buprenorphine in the Emergency Department. *Jama Netw Open*. 2020;3(5):e204996.
10. Aquino JPD, Parida S, Sofuoglu M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Invest*. 2021;41(5):425–36.

## References

11. Moe J, Badke K, Pratt M, Cho RY, Azar P, Flemming H, et al. Microdosing and standard-dosing take-home buprenorphine from the emergency department: A feasibility study. *J Am Coll Emerg Physicians Open*. 2020;1(6):1712–22.
12. Moe J, O'Sullivan F, Hohl CM, Doyle-Waters MM, Ronsley C, Cho R, et al. Short Communication: Systematic Review on Effectiveness of Micro-induction Approaches to Buprenorphine Initiation. *Addict Behav*. 2020;114:106740.
13. Brar R, Fairbairn N, Sutherland C, Nolan S. Use of a novel prescribing approach for the treatment of opioid use disorder: Buprenorphine/naloxone micro-dosing – a case series. *Drug Alcohol Rev*. 2020;39(5):588–94.
14. Ahmed S, Bhivandkar S, Loneragan BB, Suzuki J. Microinduction of Buprenorphine/Naloxone: A Review of the Literature. *Am J Addict*. 2021;30(4):305–15.
15. Randhawa PA, Brar R, Nolan S. Buprenorphine–naloxone “microdosing”: an alternative induction approach for the treatment of opioid use disorder in the wake of North America’s increasingly potent illicit drug market. *Cmaj*. 2020;192(3):E73–E73.
16. Wong JSH, Nikoo M, Westenberg JN, Suen JG, Wong JYC, Krausz RM, et al. 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. *Addict Sci Clin Pract*. 2021;16(1):11.
17. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care*. 1997 Oct;20(10):1512–7. doi: 10.2337/diacare.20.10.1512. PMID: 9314626
18. Samuels-Kalow ME, Stack AM, Porter SC. Effective Discharge Communication in the Emergency Department. *Ann Emerg Med*. 2012;60(2):152–9.
19. Schenhals E, Haldet P, Kass LE. Barriers to compliance with emergency department discharge instructions: lessons learned from patients’ perspectives. *Intern Emerg Med*. 2019;14(1):133–8.
20. McCarthy DM, Engel KG, Buckley BA, Forth VE, Schmidt MJ, Adams JG, et al. Emergency Department Discharge Instructions: Lessons Learned through Developing New Patient Education Materials. *Emerg Medicine Int*. 2012;2012:306859.
21. Engel KG, Buckley BA, Forth VE, McCarthy DM, Ellison EP, Schmidt MJ, et al. Patient Understanding of Emergency Department Discharge Instructions: Where Are Knowledge Deficits Greatest? *Acad Emerg Med*. 2012;19(9):E1035–44.



**BRITISH COLUMBIA CENTRE ON  
SUBSTANCE USE**  
400-1045 Howe St  
Vancouver BC  
V6Z 2A9  
[www.bccsu.ca](http://www.bccsu.ca)

