
BRITISH COLUMBIA
CENTRE ON
SUBSTANCE USE
Networking researchers, educators & care providers
Buprenorphine/naloxone in the ED
– Approach to Microinductions
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*We respectfully acknowledge the land on which we work is the unceded traditional territory of the Coast Salish Peoples, including the traditional territories of xʷməθkwəy̓əm (Musqueam), Sḵwx̱wú7mesh (Squamish), and Sḵ̓ílwətaɬ (Tsleil-Waututh) Nations*

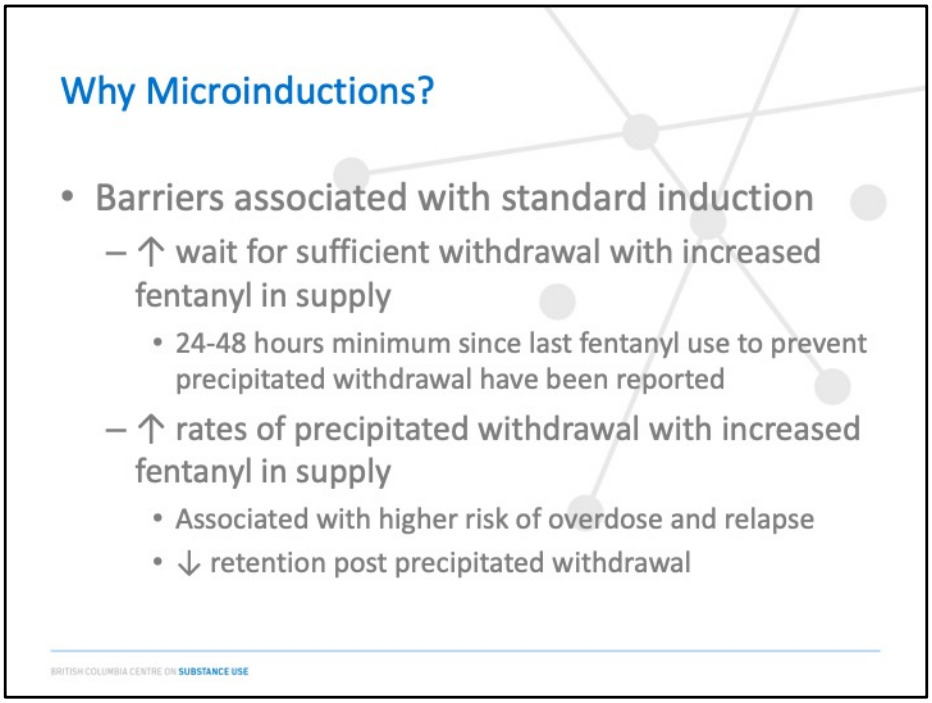
## Disclaimer

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.

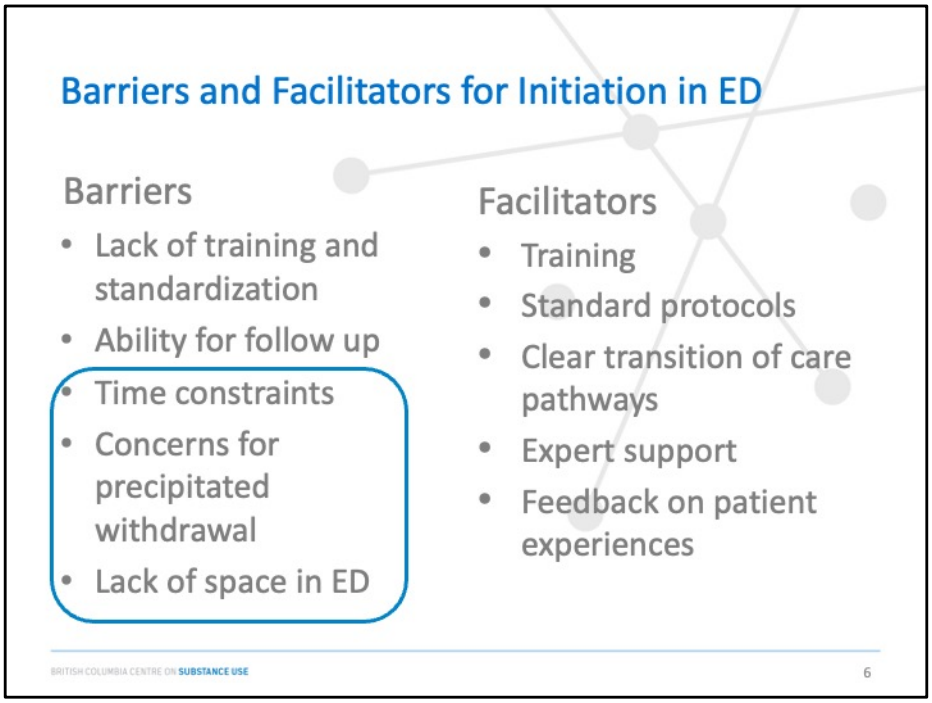
This includes innovative and novel approaches specific to emergency settings that are based on clinical experience. There is currently little evidence or research into the effectiveness of some of these protocols, therefore clinical judgement is advised.

## 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




Changes to the illicit supply have lead 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
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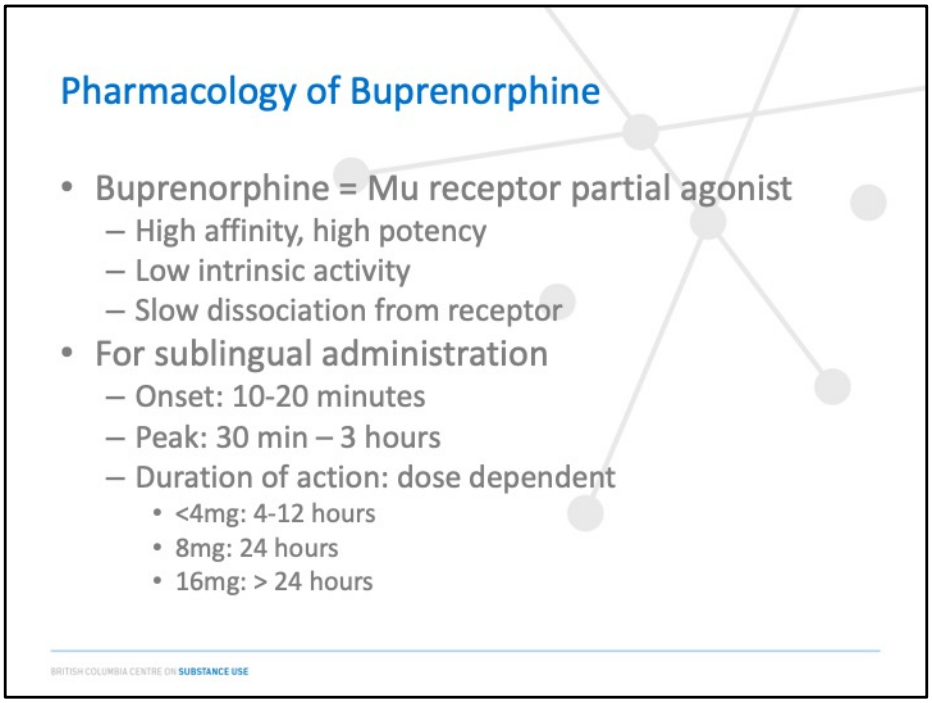
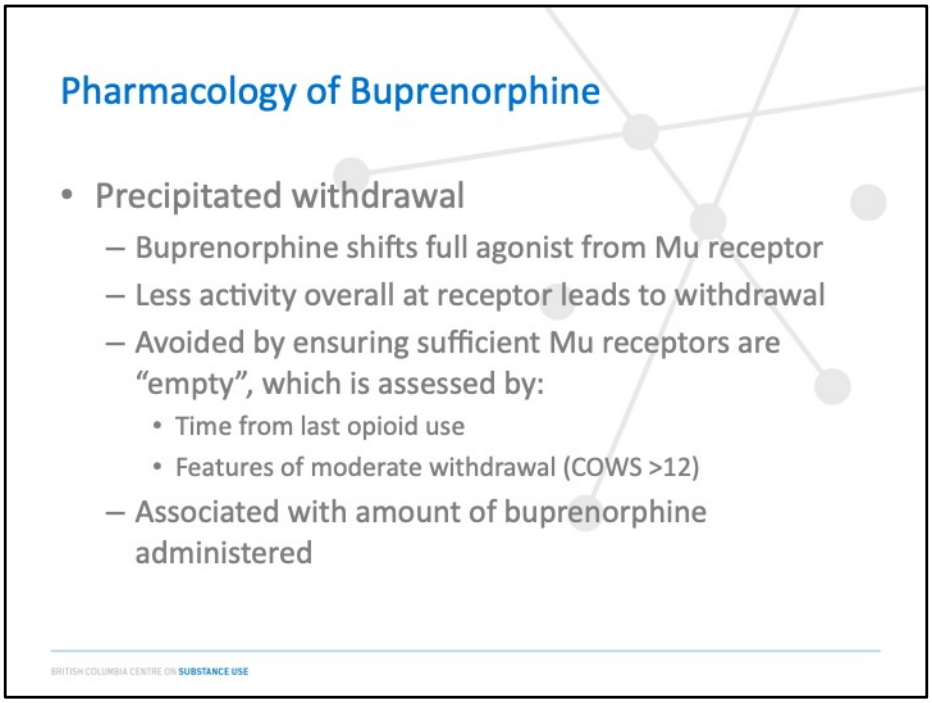



As more is appreciated about buprenorphine's pharmacology, its acknowledged that how it interacts with various receptors to produce a clinical effect is more nuanced than previously recognized.

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.

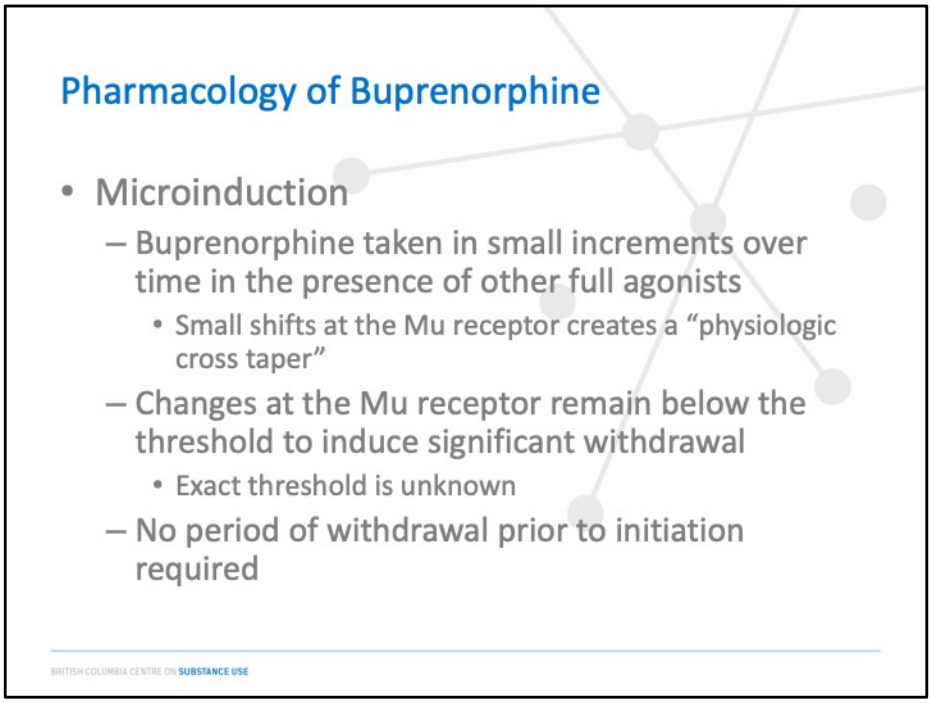



Buprenorphine, when taken in the presence of other full opioid agonists, will displace the full mu agonist from the receptor and create overall "less activation" of the mu receptor. This presents clinically as rapid onset of moderate-severe withdrawal.

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.

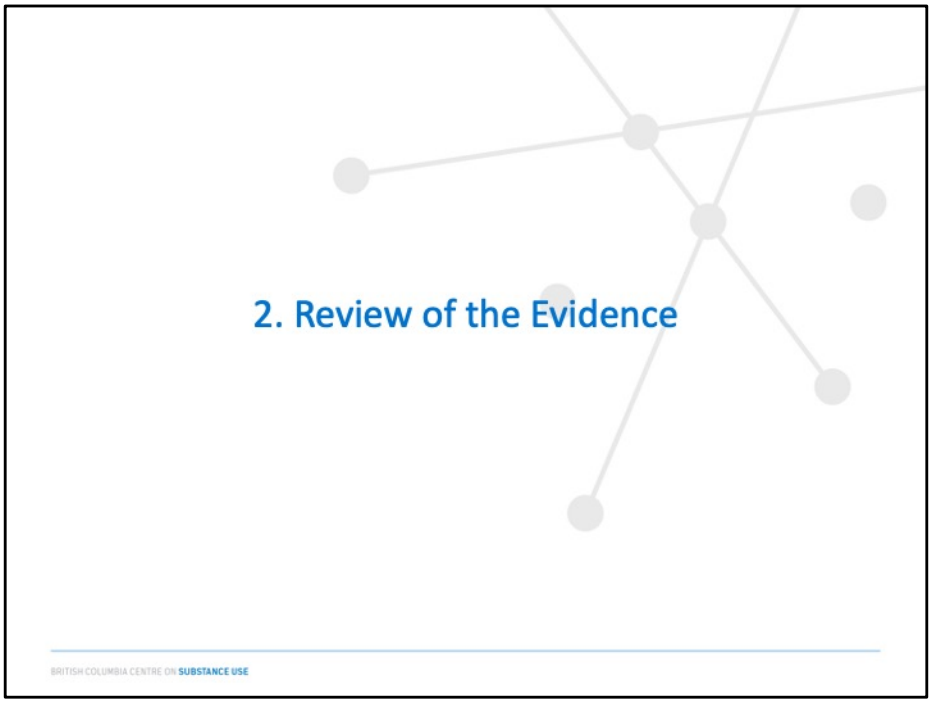
The severity and duration of precipitated withdrawal (remember slow dissociation) is related to the amount of buprenorphine administered.

COWS = clinical opiate withdrawal scale




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
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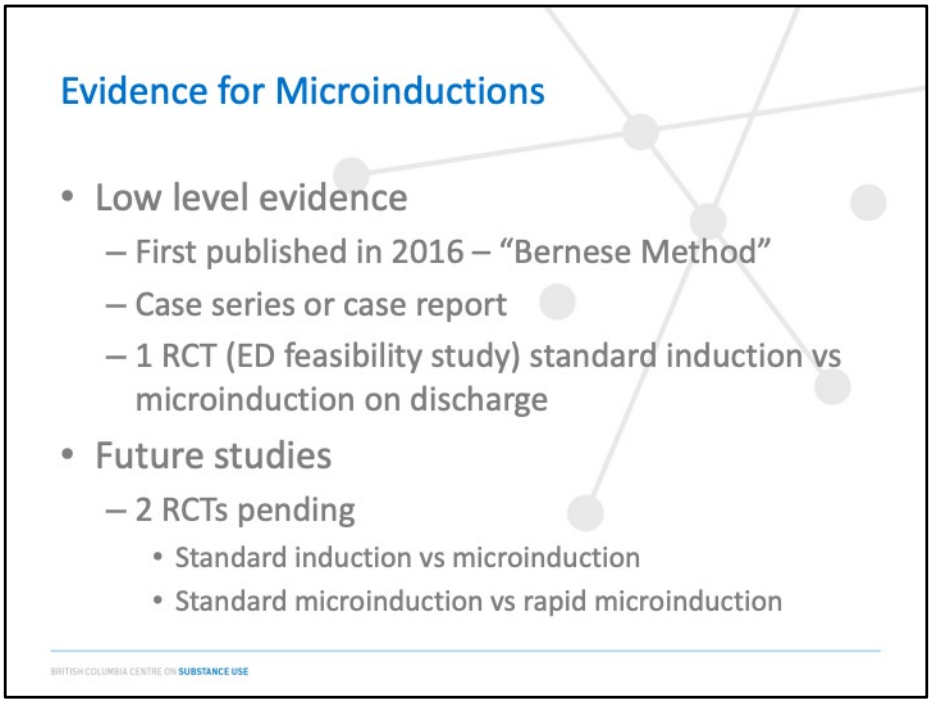
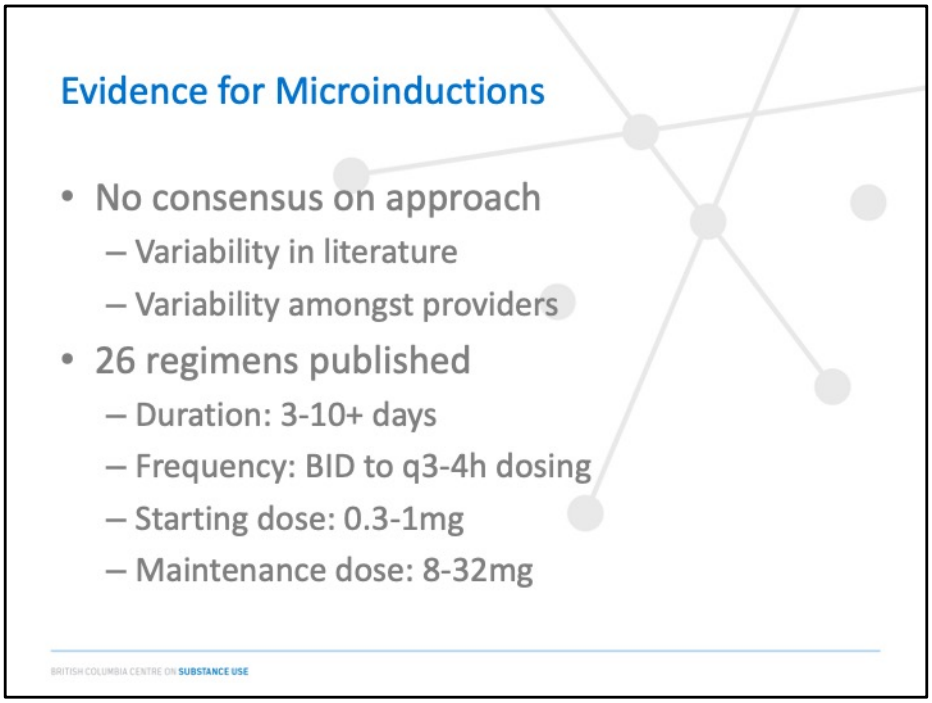


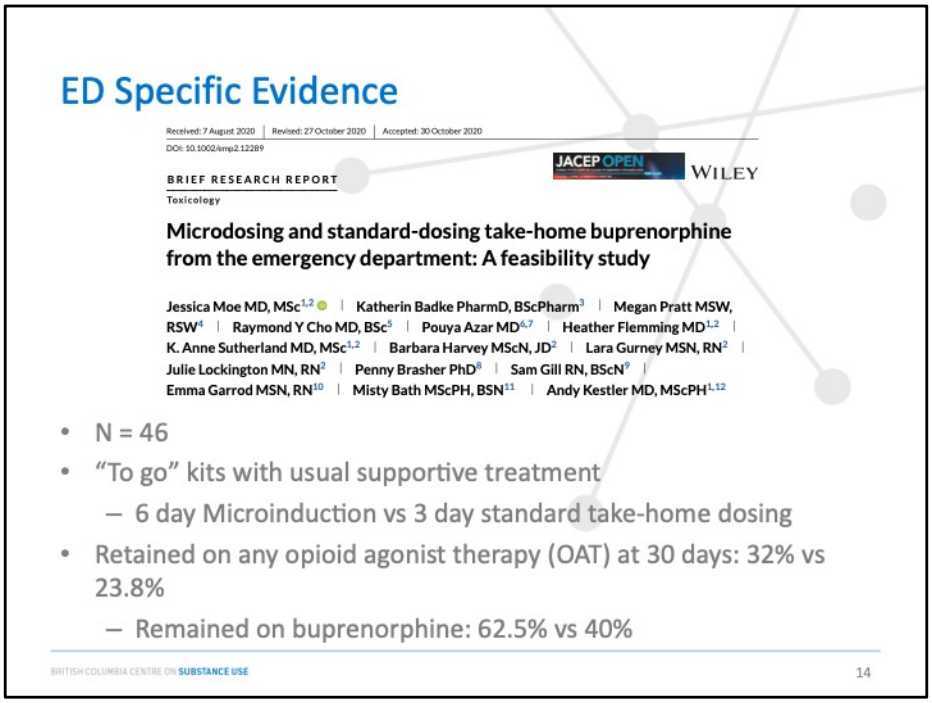

First published in 2016 by Bernese et al, the theory for microinductions was based on prior studies showing low doses of IV buprenorphine (0.2mg) did not precipitate withdrawal in patients already on methadone and prior studies showing that small escalating doses of an opioid antagonist caused attenuation 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:

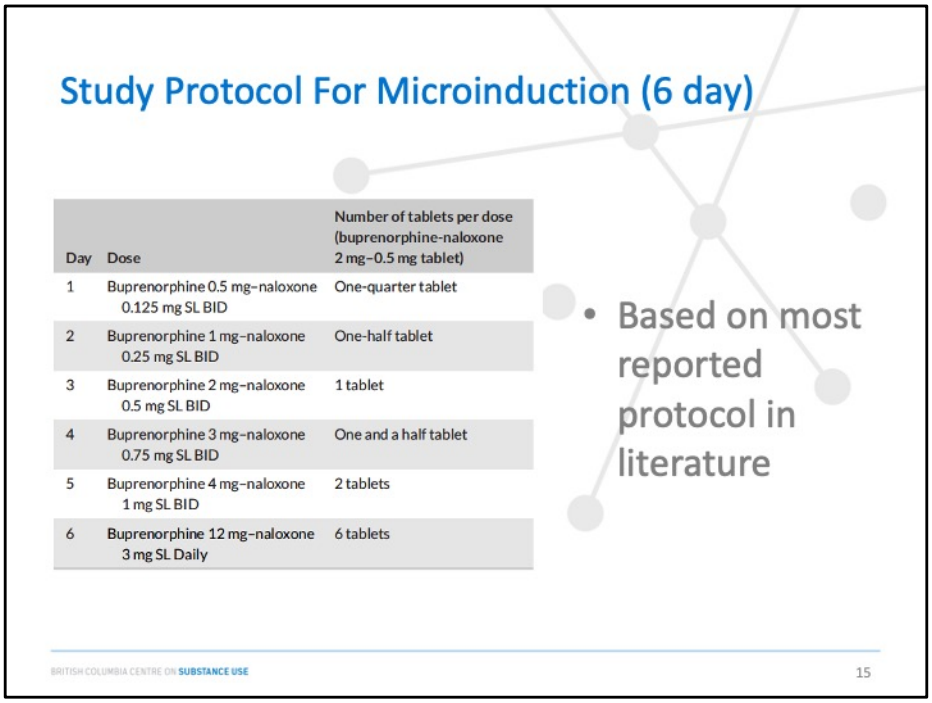
- The first will be comparing microinduction to standard induction on a larger scale from the ED.
- The second will be comparing a standard microinduction to a more rapid protocol in an inpatient setting.
- We will review what these protocols are later in this module.



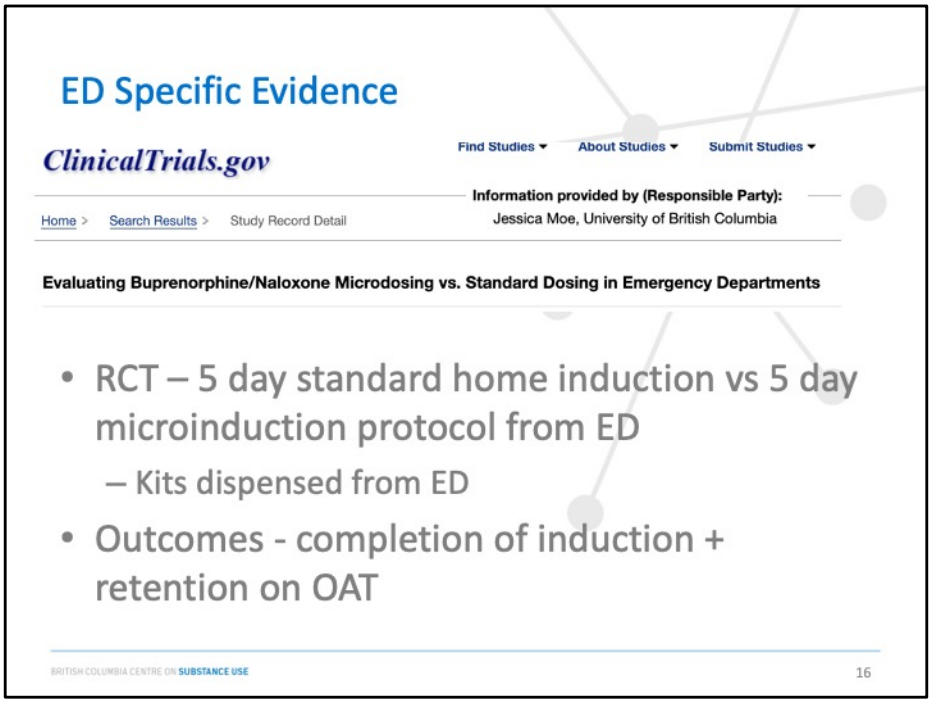

- There is a lot of variability in approaches to microinductions, both in the literature and in current clinical practice.
- This wide range of methods is based on differences in frequency of doses and rapidity of escalating dose amounts, as highlighted in the slide.
- The aim is to consolidate to a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



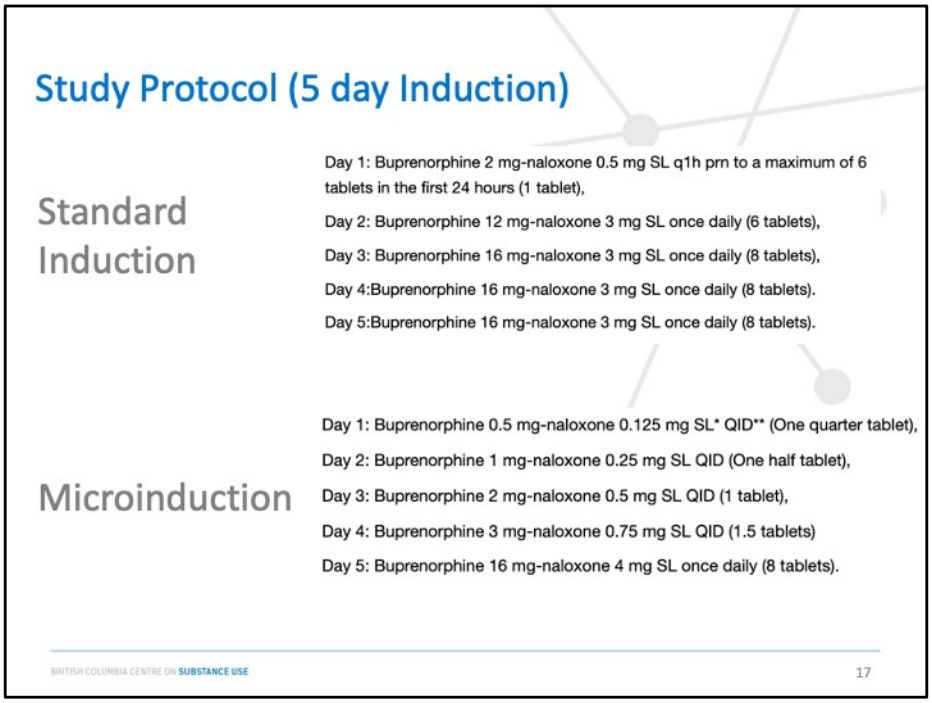

The only RCT published to date comparing microinductions to standard inductions was this feasibility study from the ED.
When comparing to go kits dispensed from the ED on patient discharge, the microinduction arm showed higher retention rates on buprenorphine at 30 days.



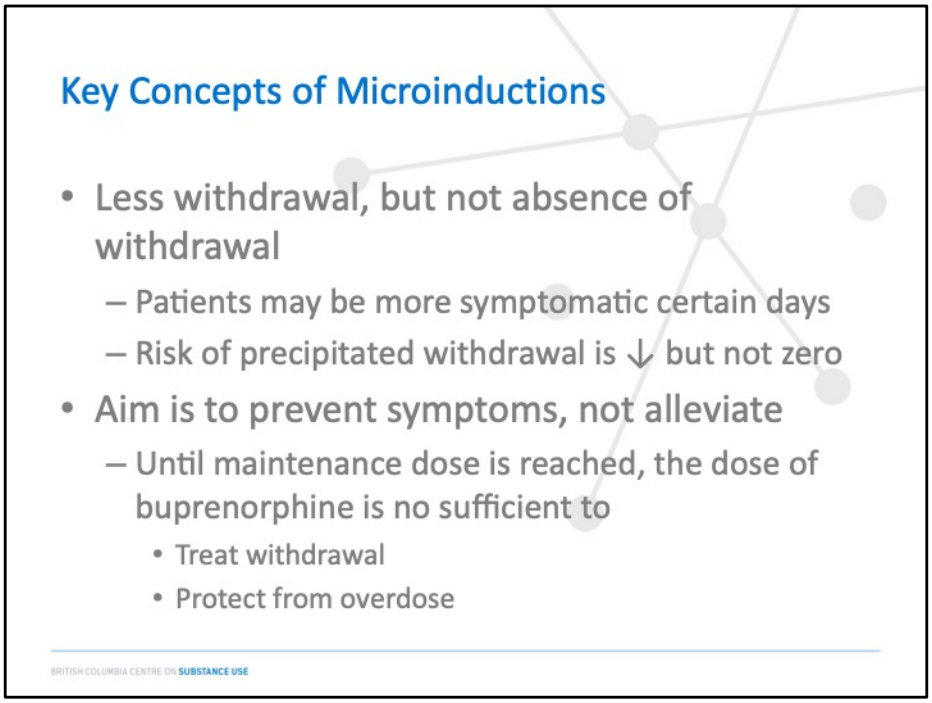

Their microinduction protocol was based on the most common protocol published in the literature.




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




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




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

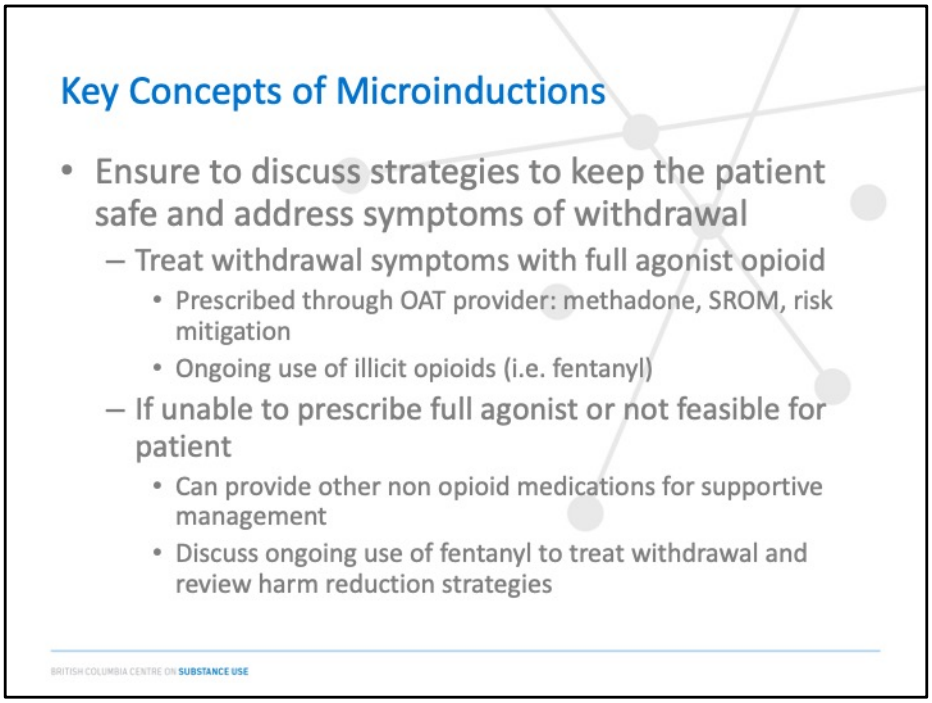
<u>Patients will feel less withdrawal, but not complete absence of withdrawal symptoms</u>

- 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.

<u>The aim of microinductions is to prevent risk of precipitated withdrawal, not alleviate withdrawal</u>

- 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.




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.

<u>This is often not available or feasible to ED physicians:</u>

- 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.

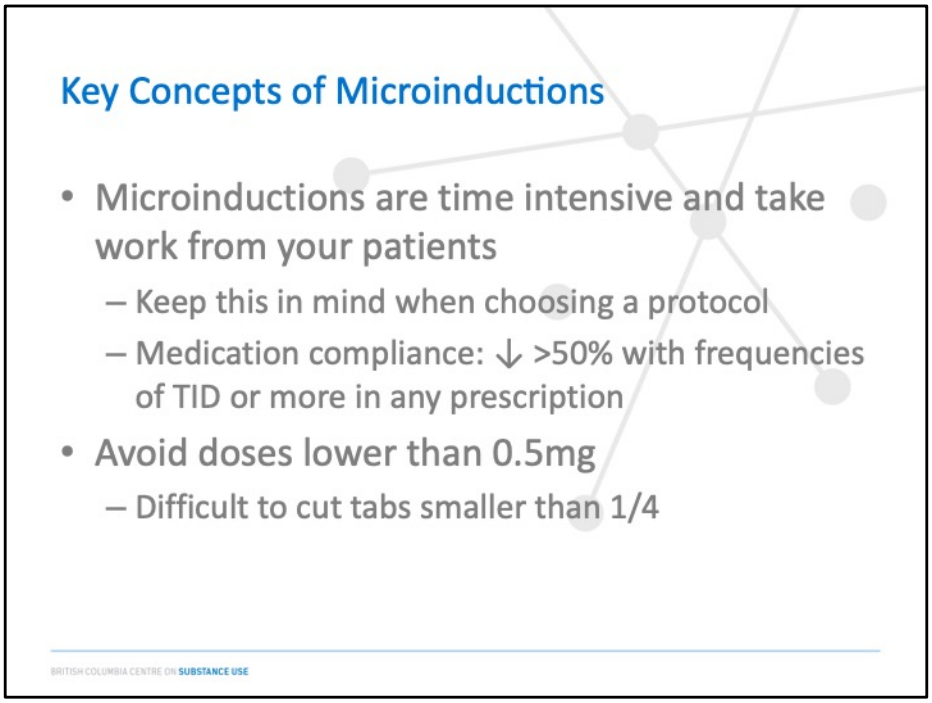
<u>ED providers can support patients by</u>

- 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).

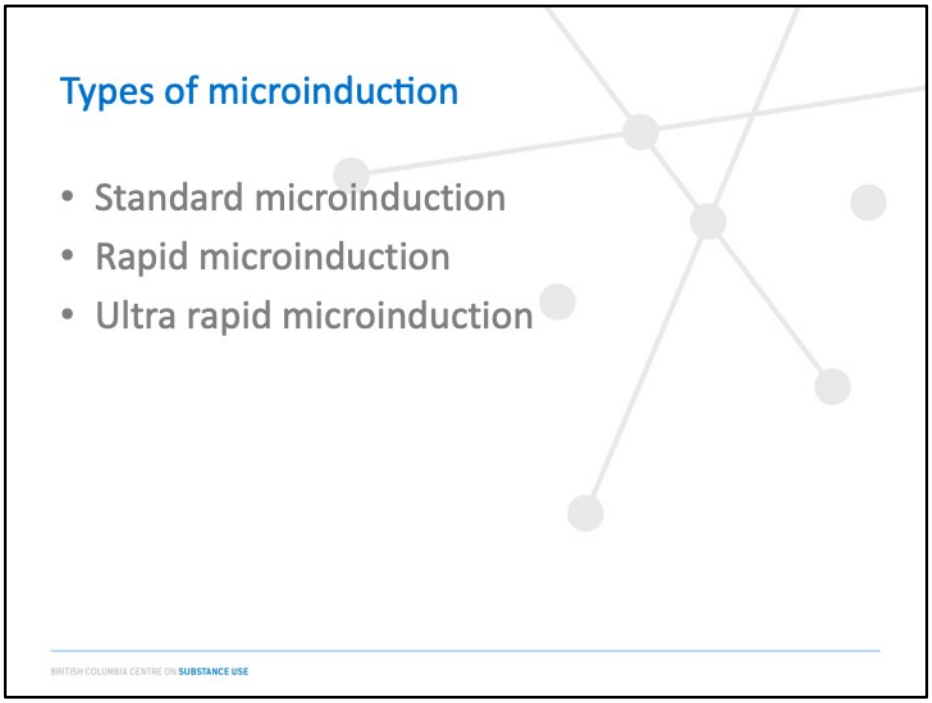
- Review harm reduction and safer use of illicit opioids (see module on harm reduction)
- Can consider prescribing medications that would be used for symptomatic management during a standard induction, such as clonidine, acetaminophen, NSAIDs etc.

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

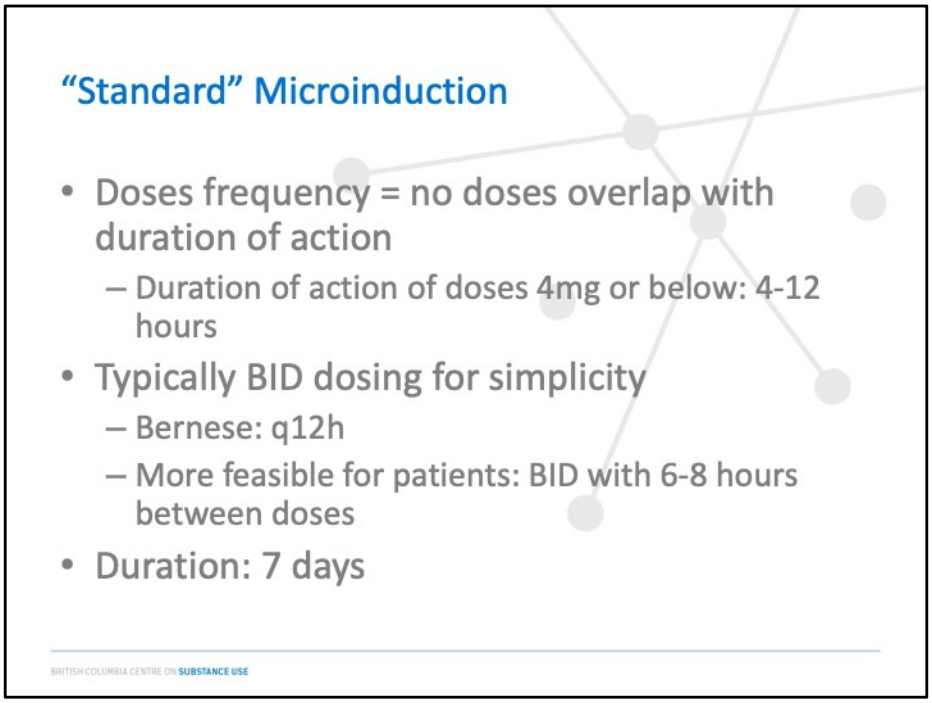



Microinductions require patients to keep track of doses, while treating their withdrawal – this can be a time intensive process for many.
Although no protocols have been compared head-to-head, keep in the mind your patient's setting and stability when choosing the frequency of dose administration. In 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)*

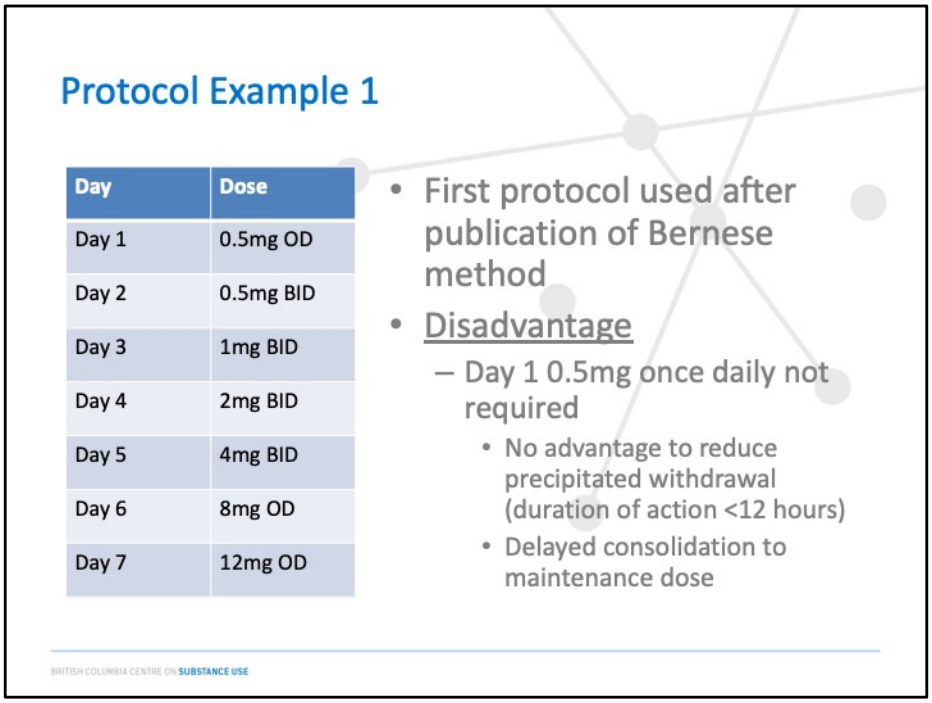
Some protocols start at ever lower doses (0.25mg). However, this is not practical in most settings – 2mg tabs cannot be cut consistently when cut smaller than in ¼.



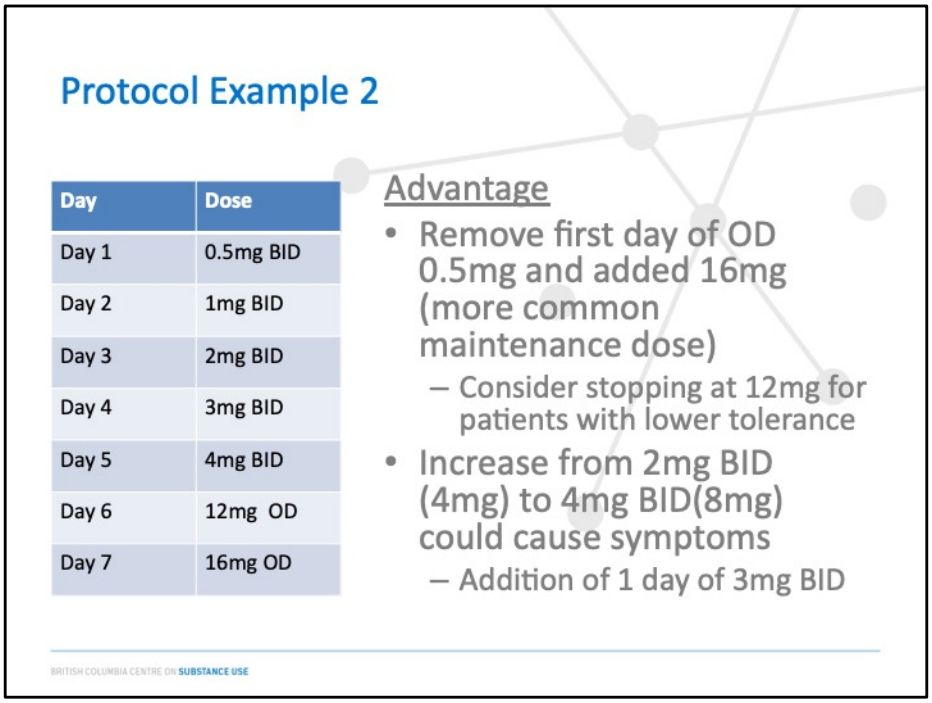

Protocols vary along a spectrum of duration and rapidity of dose escalation/frequency.
For simplicity, we will review 3 broad categories, with recognition that there is significant overlap between each.




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.

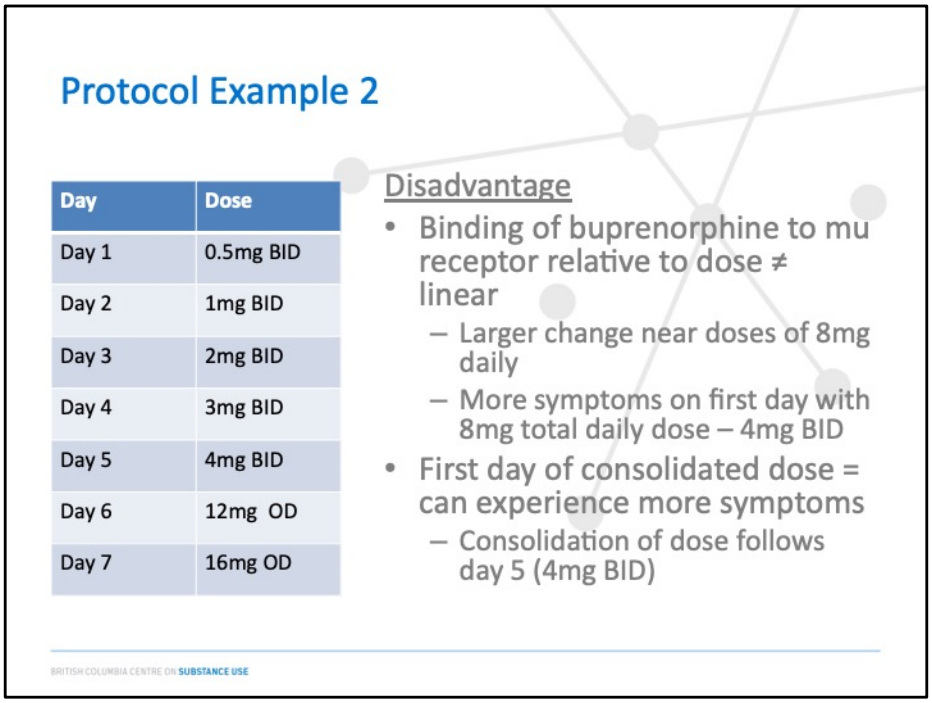



This protocol was more common initially after the Bernese method was published. It was noted in clinical application that the first single dose of 0.5mg was not required to prevent precipitated withdrawal but delayed ultimately consolidation to maintenance dose.



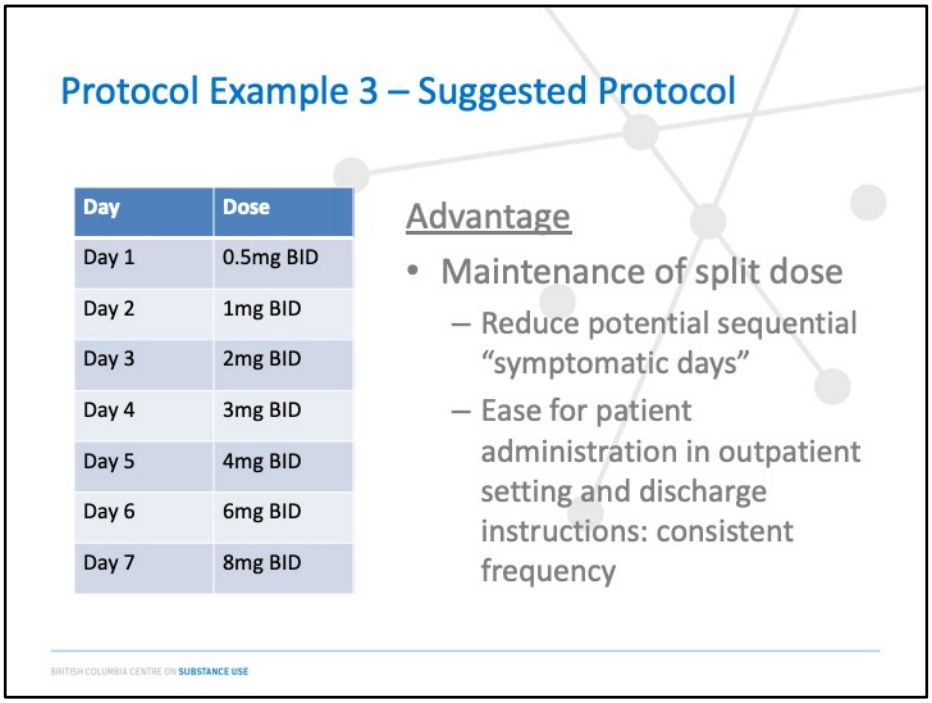

This second iteration was adjusted to reflect this clinical practice.
It was also noted that the jump from 2mg BID (4mg) to 4mg BID(8mg) from the previous protocol was often too quick for patients and lead to increased symptoms. An intermediary day was added with 3mg BID.

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.

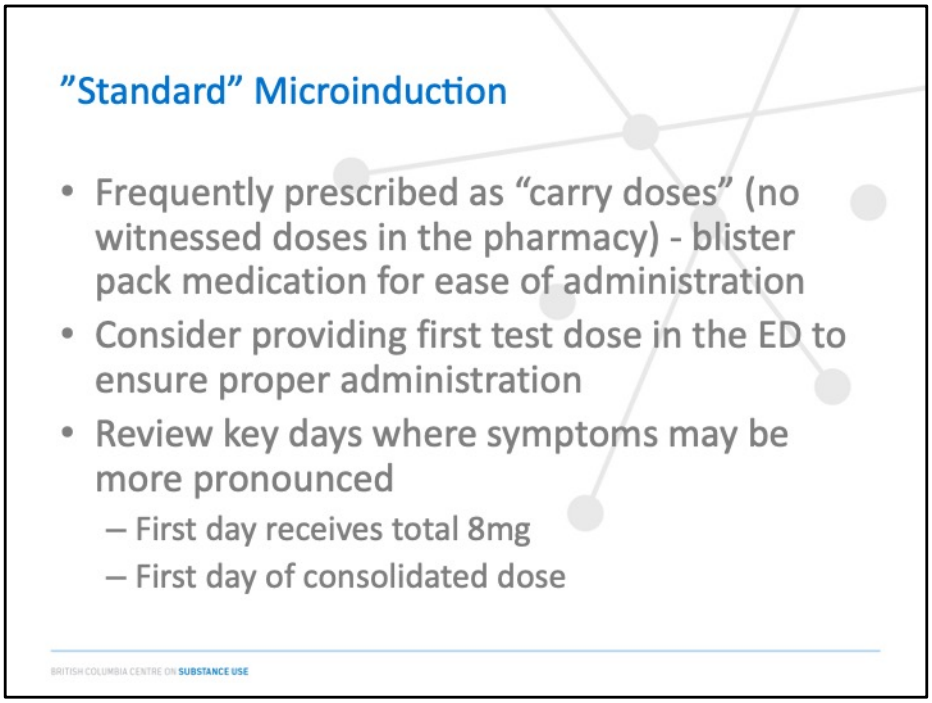



There are two days where patients may feel more symptomatic during this protocol

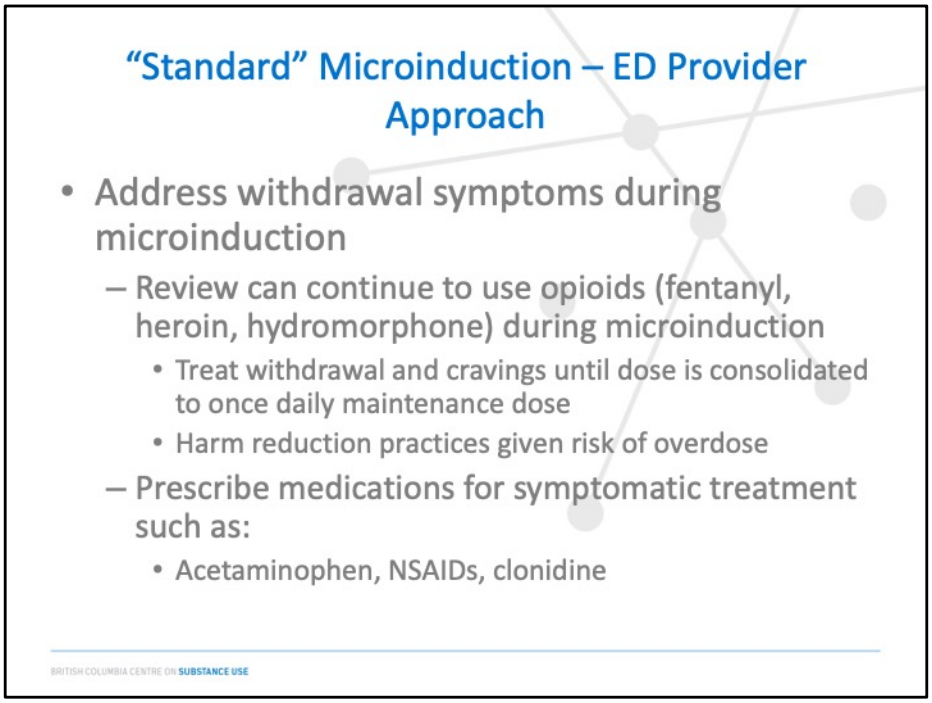
1. Anecdotally, patients feel more withdrawal symptoms during day 5 of the last 2 protocol, where you can see the total daily dose equals 8mg (4mg BID).
    - Binding to the mu receptor by buprenorphine is not linear. There are more significant changes when doses near 8mg total daily.
2. The second is 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.



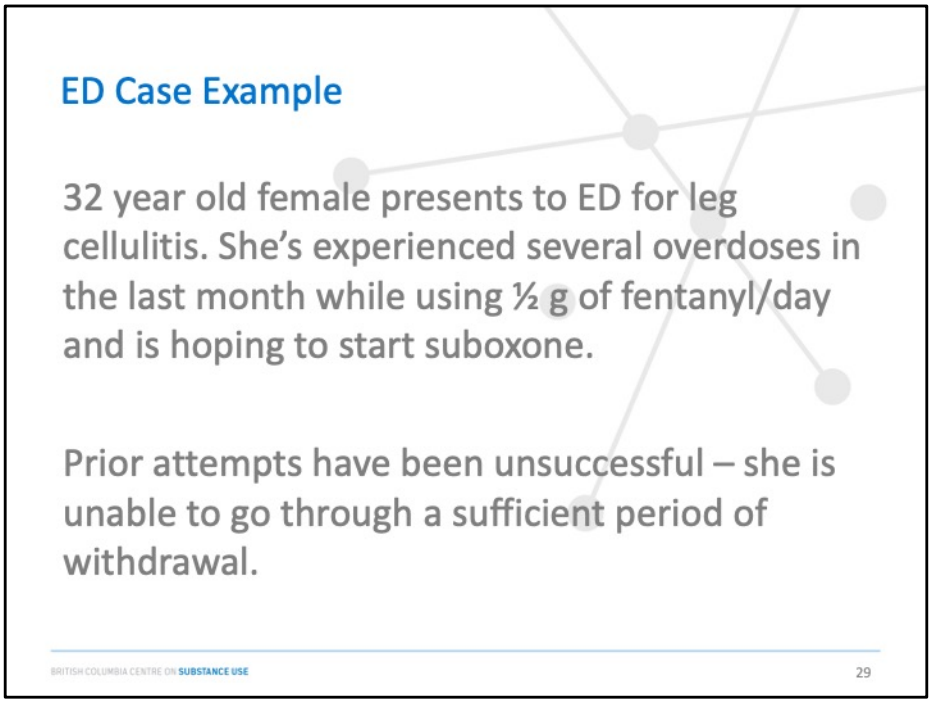

This third example addresses prior concerns by continuing split (BID) dosing throughout.
Consolidation to 16mg occurs after completion of the microinduction (day 8).
It also offers the advantage of consistent dosing for ease of patient instruction and compliance.




- 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.




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.

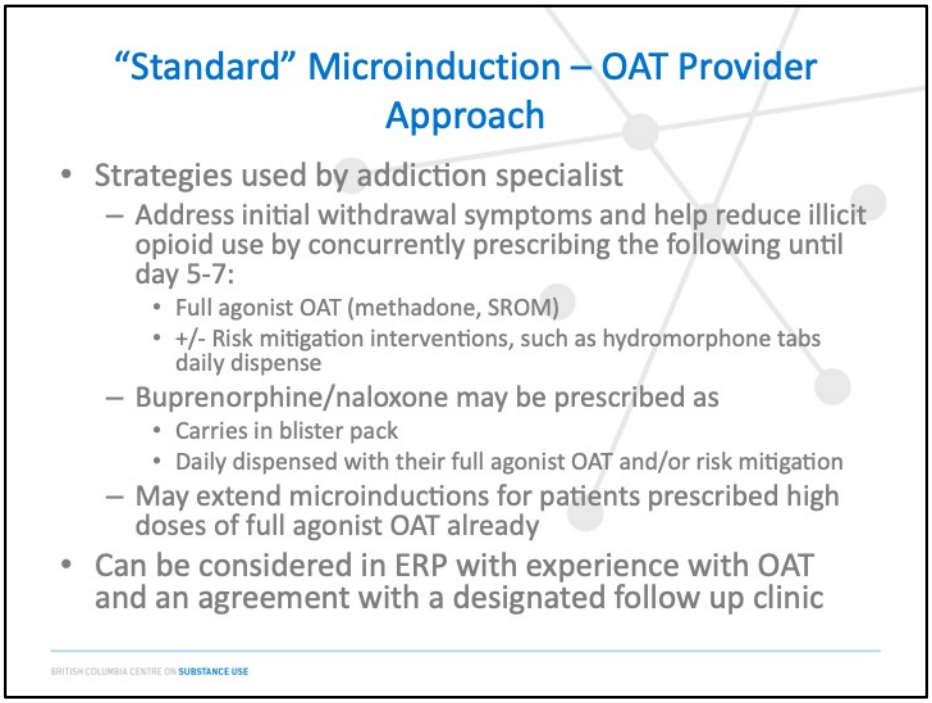



How does this look practically on shift? Let's look at a case example.

## 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 |




**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<br>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 | |

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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 |

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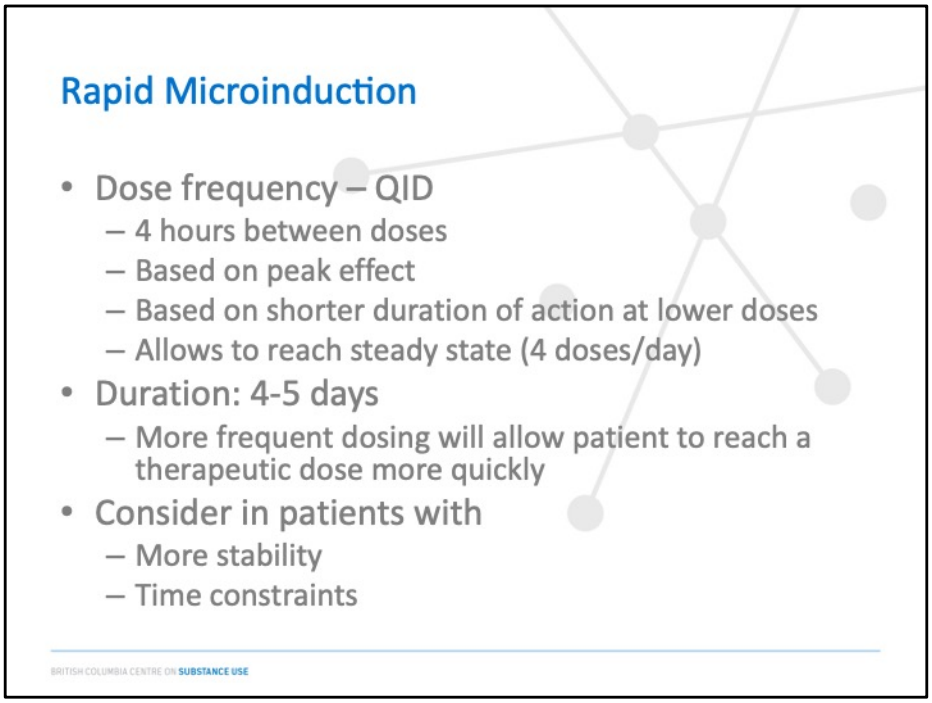
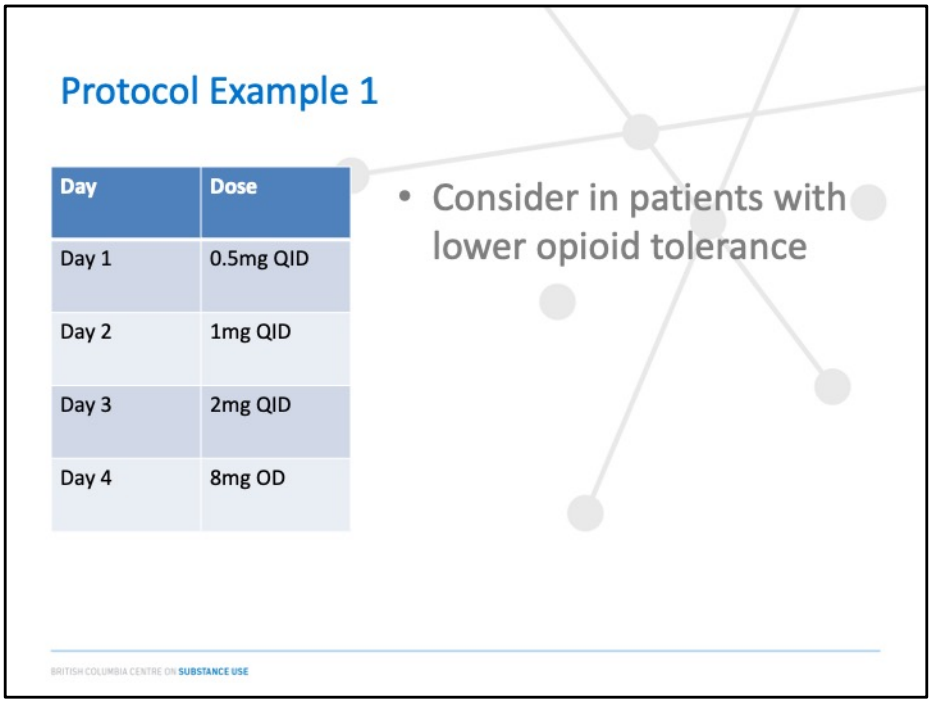
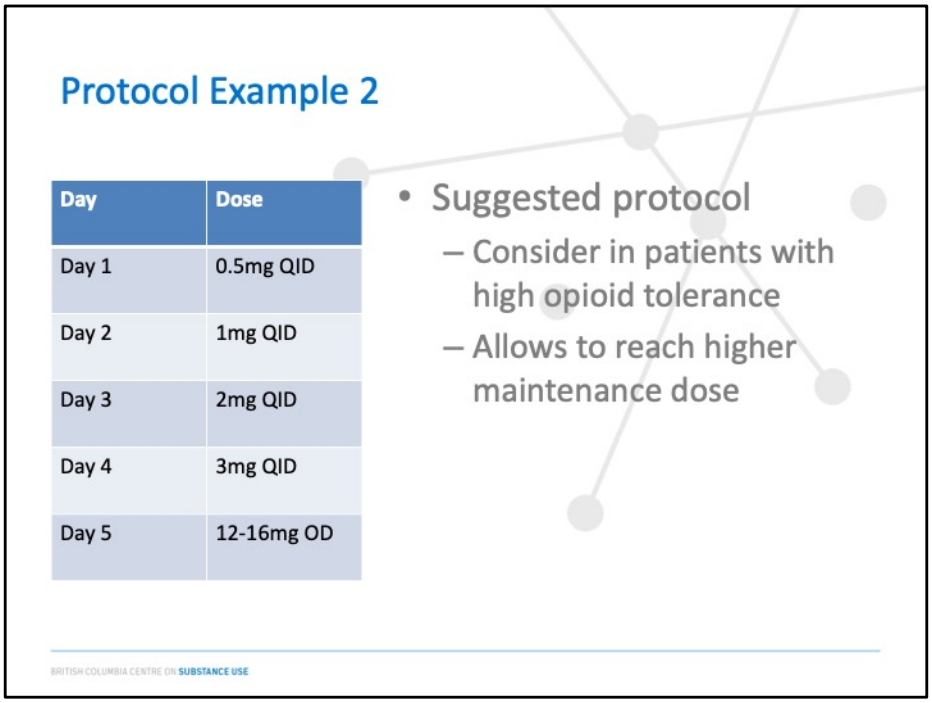
This is a case example where the patient would present already on a maintenance dose of methadone (120mg).



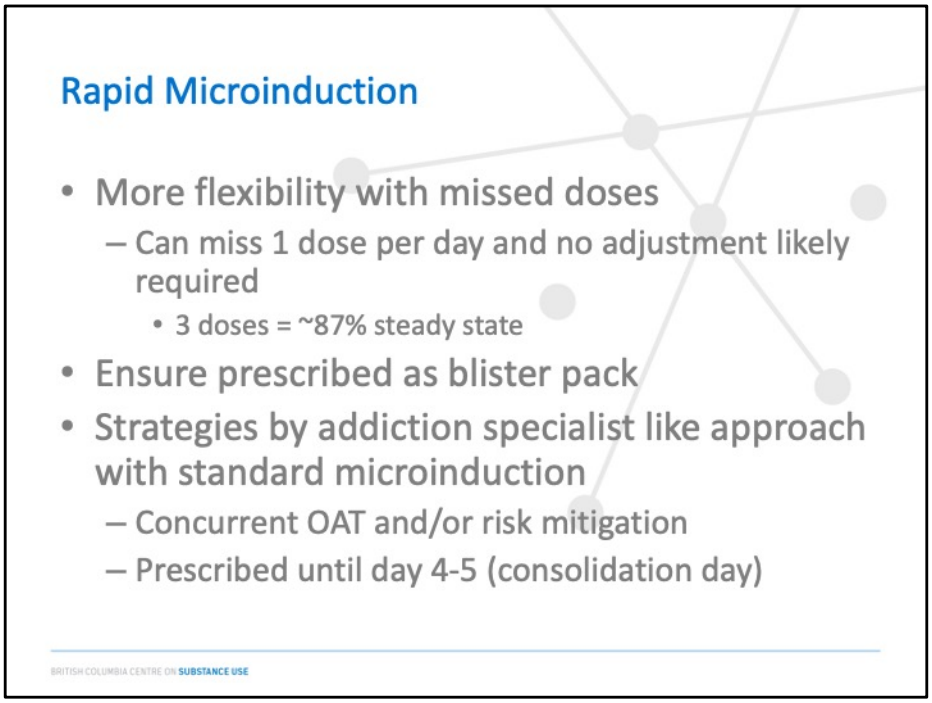

A rapid microinduction structures its frequency based on the shorter range of duration of action (4 hours) and on peak effect of buprenorphine (3 hours for the longest estimate).
QID dosing (with 3-4 hours between doses) allows for steady state to be established for each dose (4 doses per day), and for 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).



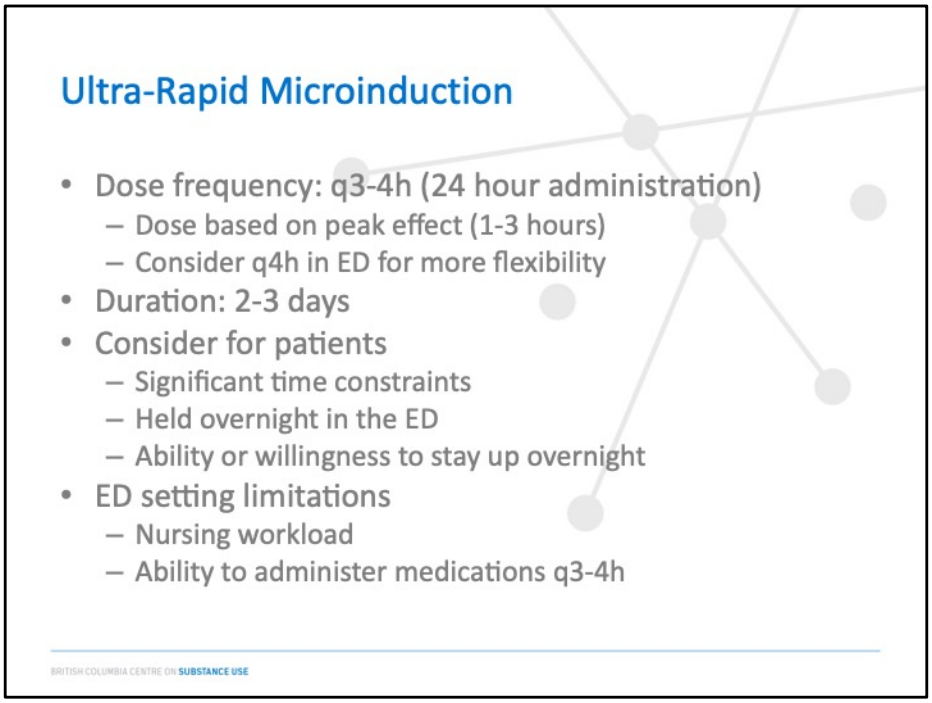

This protocol consolidates to 8mg. This can be considered for patients with lower opioid tolerance, given most will require dose of 12-16mg at minimum to reach stability.




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.

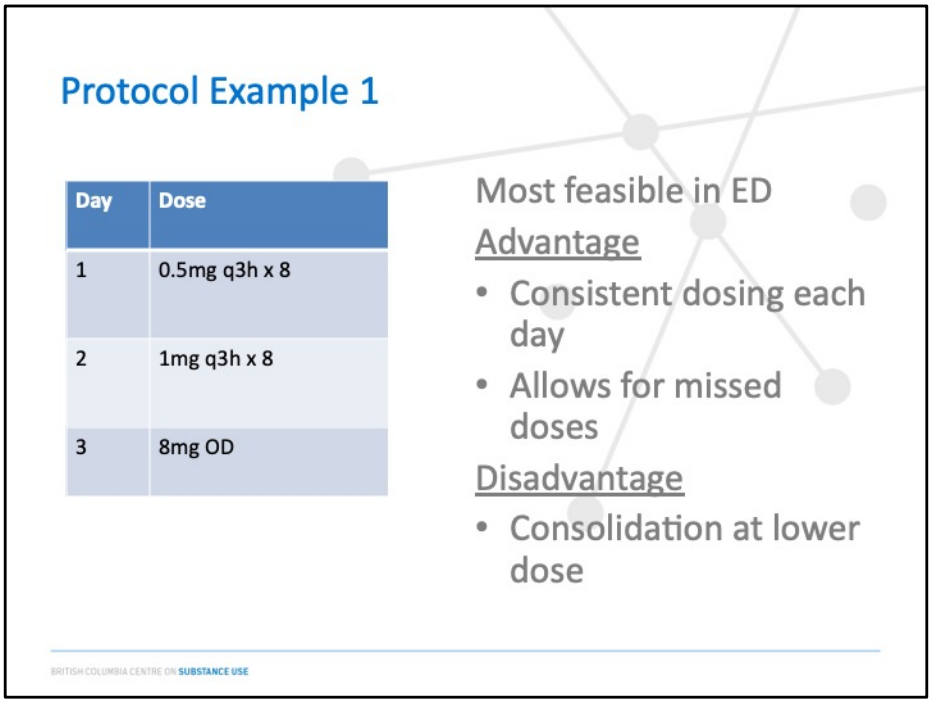



The rapid microinduction allows some flexibility with missed doses relative to the standard induction.
If the patient receives 3 doses, they are likely at sufficient steady state to proceed (estimated 87%).
Given the higher technical requirements for the patient, blister pack is always recommended to facilitate completion.
Strategies to treat withdrawal during these rapid microinductions are like standard induction – please see previous slide outlining this in more detail.




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 a 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.




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

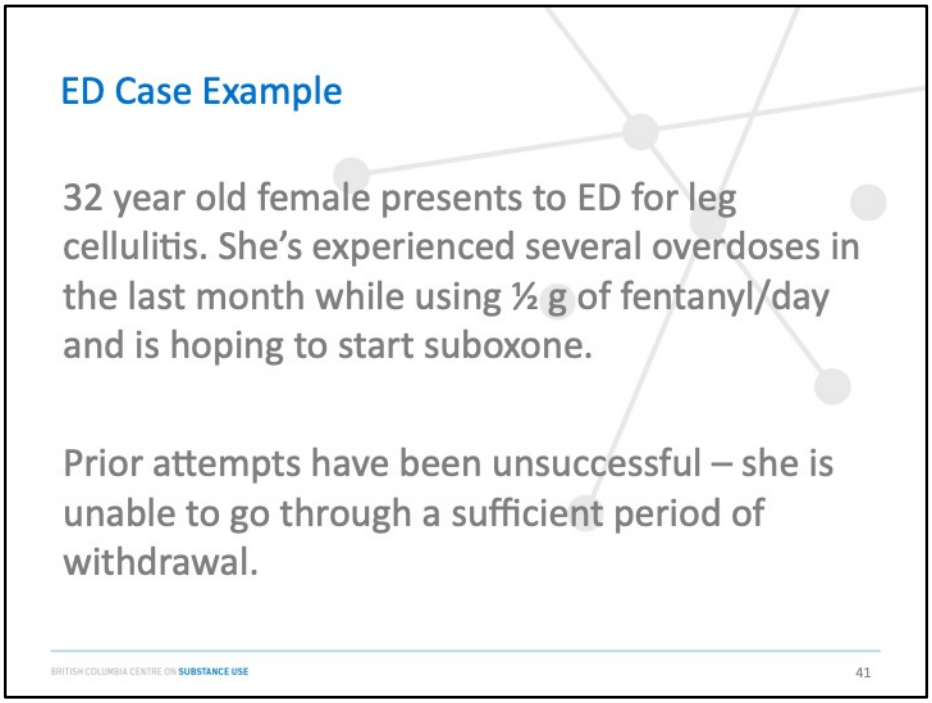
| Day | Dose |
|---|---|
| 1 | 0.5mg q3-4h x 4 doses<br>1mg q3-4h x 4 doses |
| 2 | 2mg q3-4h x 4 doses<br>3mg q3-4h x 4 doses |
| 3 | 16mg OD |

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

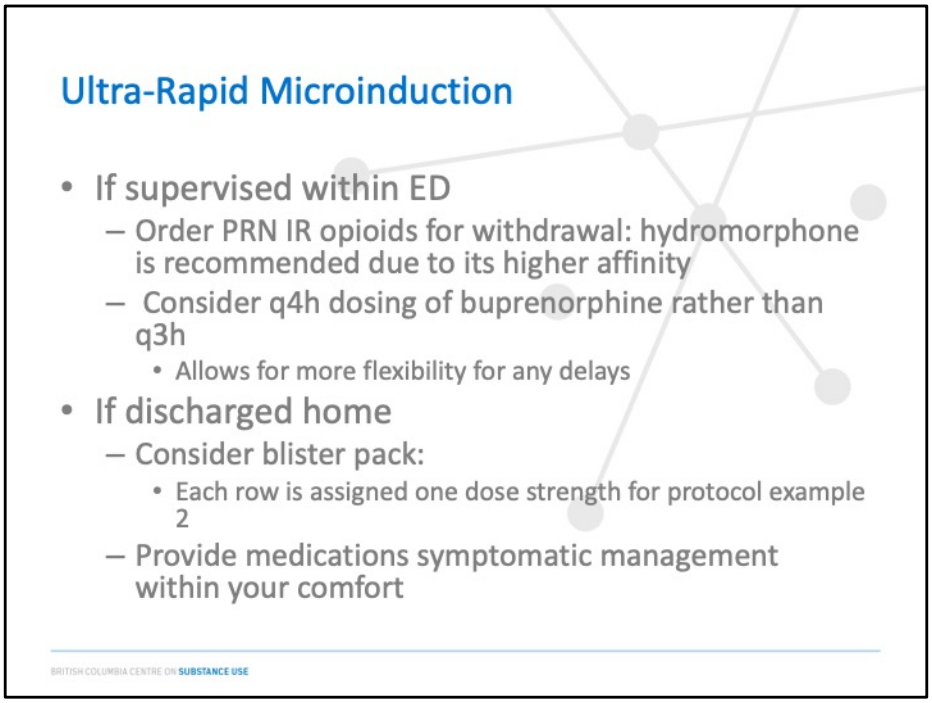



Similar to our case from earlier, but this time our patient is being held overnight for further monitoring.

## 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

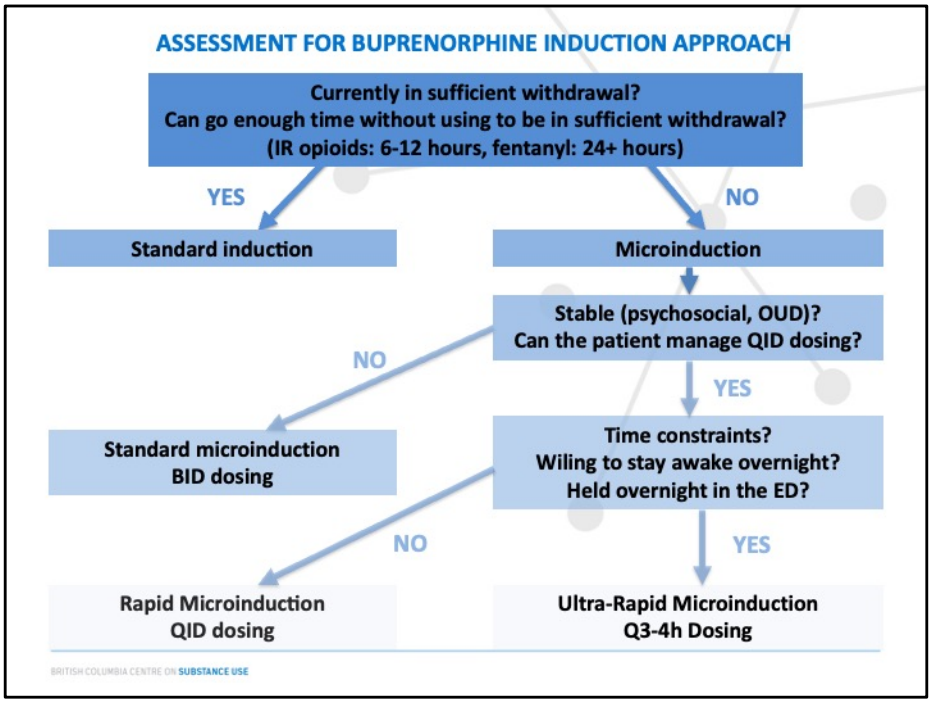



<u>In the ED (acute care)</u>

- 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.

<u>Outpatient setting (discharged home)</u>

- 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

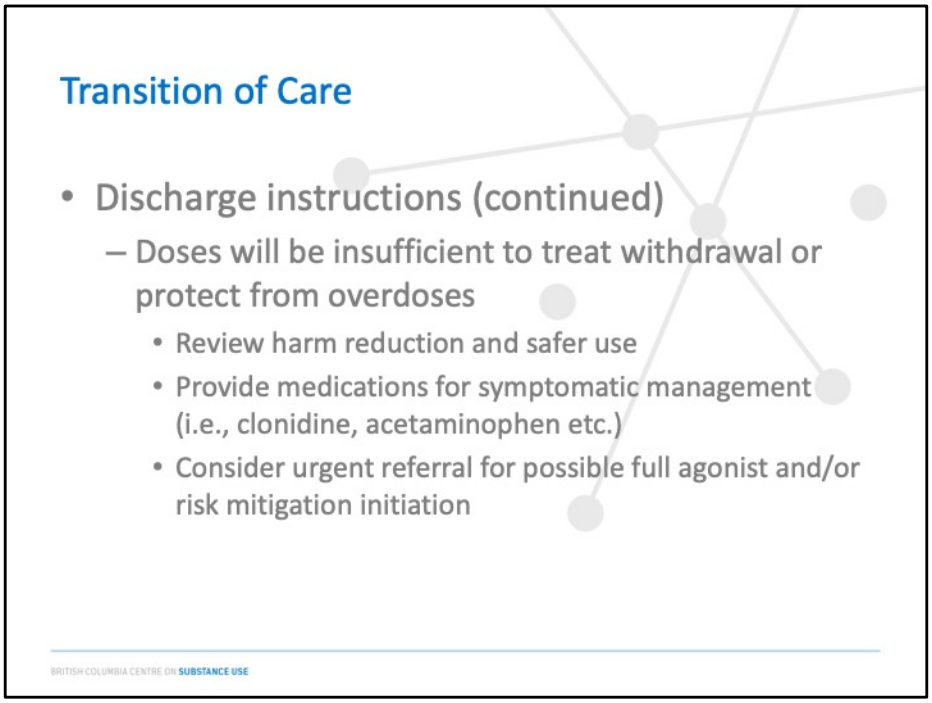
- Clear pathway, and low barrier referrals for community follow up
- Discharge instructions – patient dissatisfaction linked with decreased likelihood of filling prescription
  - Written instructions/information sheet
  - Patient-centered language = better understanding (e.g. number of pills to take, 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




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

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