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Using Micro-Dosing to Convert Patients From Methadone and Other Full Agonist Opioids to Buprenorphine/Suboxone

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University of Idaho ECHO presentation

The speaker has no relevant financial relationship(s) to disclose.

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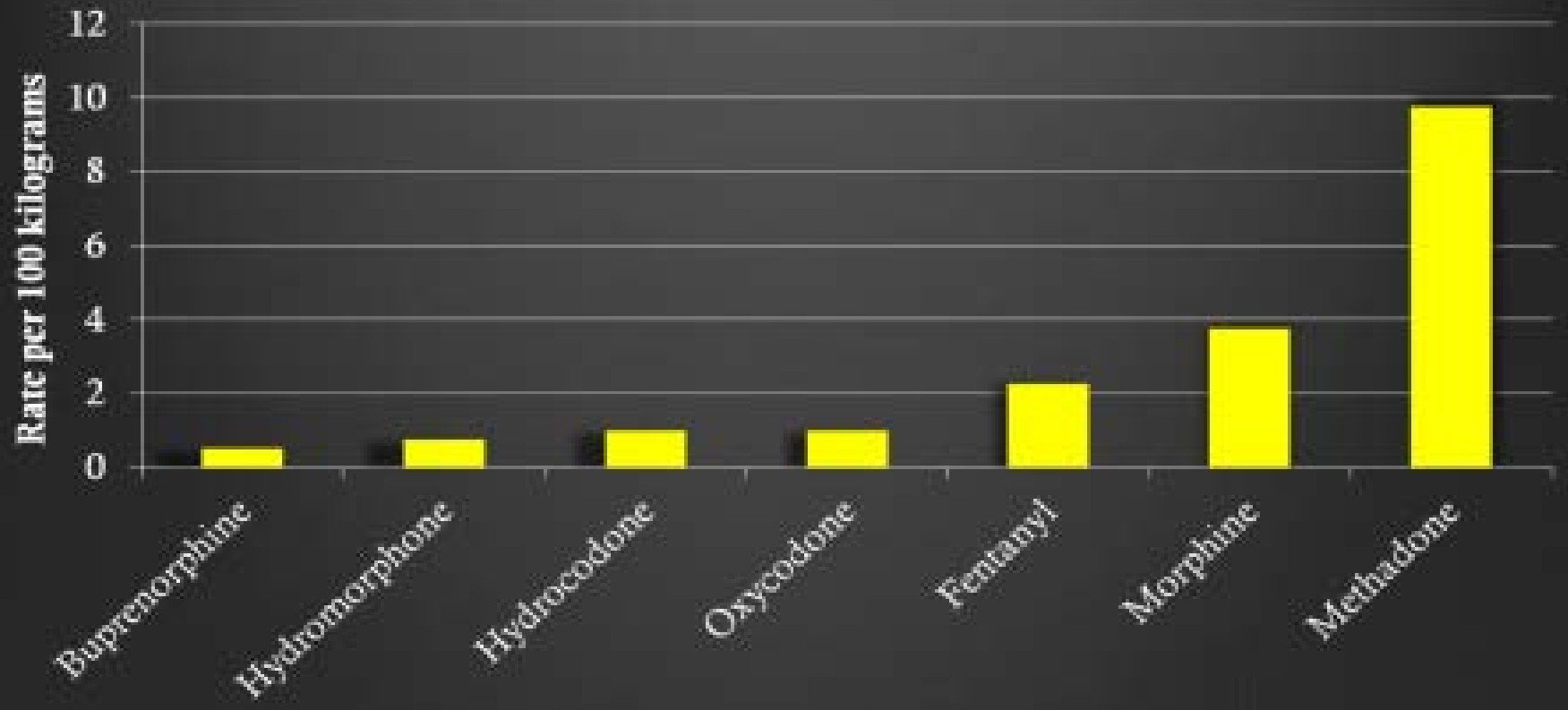
Learning Objectives

- 1) Be familiar with some potential problems with Methadone
- 2) Understand the general concepts of microinductions
- 3) Be familiar with different microinduction regimens
- 4) Be familiar with the possible advantages and disadvantages of microinduction

Methadone issues

- 6 times the risk of accidental overdose compared to Buprenorphine. Other full agonists have comparable increases.
- 1/3 of all opioid related deaths in the United States related to Methadone.
- Unpredictable pharmacokinetics
- Idiosyncratic response
- Long half life (128 Hours)
- QT prolongation
- Can act as an NMDA receptor antagonist, blocking the excitatory neurotransmitter, Glutamate. Some similarities to ETOH, Benzos, and Barbiturates with withdrawal.

Death Rate from Overdose Caused by a Single Prescription Painkiller



Adapted from: Substance Abuse and Mental Health Administration, Center for Behavioral Statistics and Quality, Drug Abuse Warning Network Medical Examiner Component, 2009

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Issues with converting to Buprenorphine

- Replacing methadone which is a full agonist with Buprenorphine a partial agonist with higher receptor affinity will knock methadone off of the receptor and precipitate sudden withdrawal.
- Some risk factors for this are high Methadone dose, short time to conversion, and female gender

Can take as much as 96 hours off of Methadone to get to a level of where this does not happen.

We can do this gradually with microdosing and “bridging”

- This consists of starting off with very low doses of Buprenorphine with gradual increases and allowing it to take over the Mu receptors.
- Eliminate patients having to go through withdrawal.
- Can help prevent an increase in pain during the induction phase.

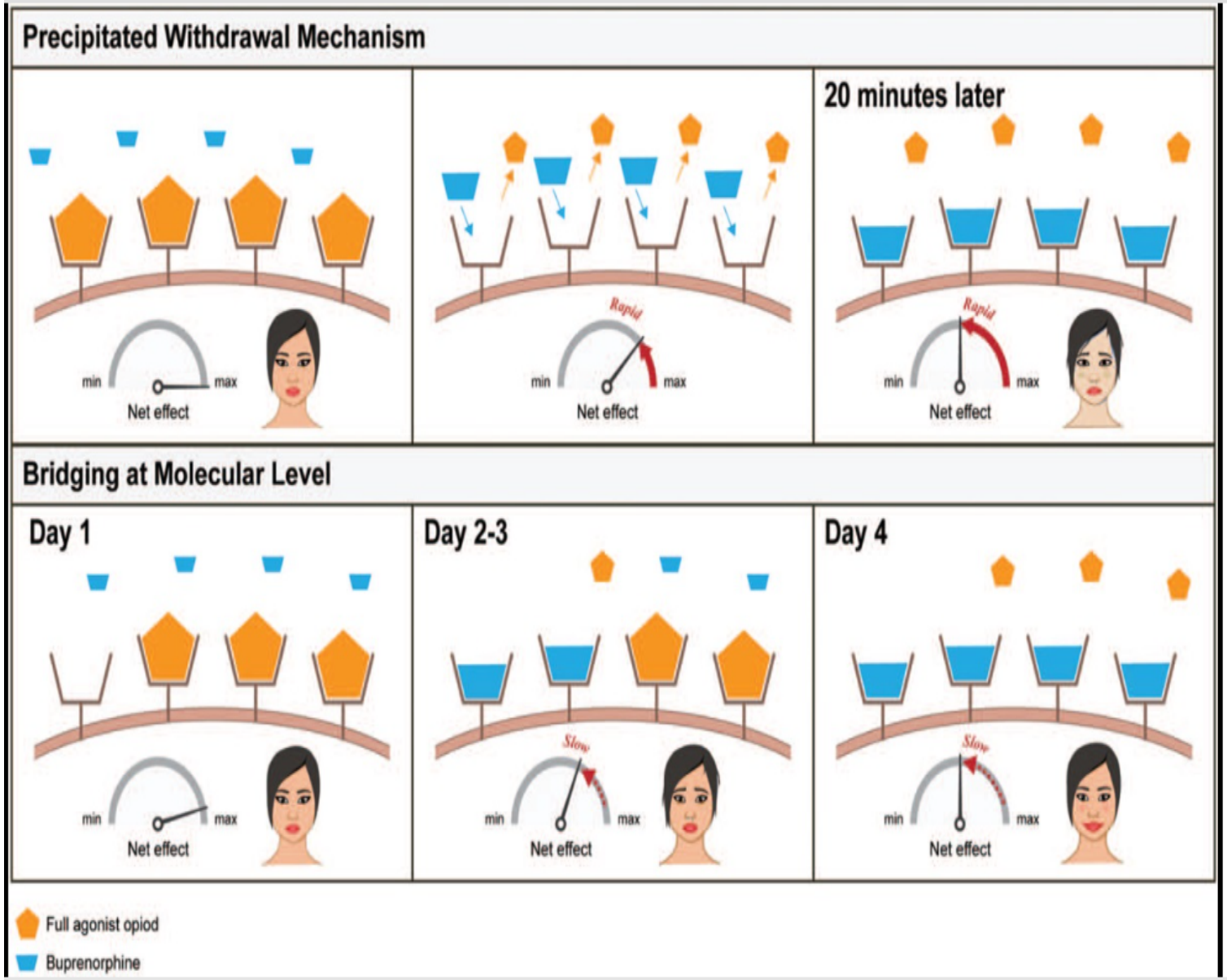

FIGURE 1

Mechanism behind precipitated withdrawal mechanism as well as bridging: Partial agonist opioid with high affinity for μ-receptors replaces the full opioid agonist rapidly over a short period of time causing a massive change in the net μ-receptor activation leading to rapid precipitated withdrawal. This can be mitigated by bridging, where the gradual introduction of higher affinity partial agonist opioids can help minimize withdrawal symptoms.

Source

A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist

Let’s look at different induction methods

- What we’ve typically done:
  - Taper Methadone dose to 30 mg or less (or maybe 40)
  - 36-72 hours off of methadone with patient presenting in withdrawal
  - Start induction with small doses of Buprenorphine and titrate upwards to alleviate withdrawal symptoms and/or pain.
    - Typically this involves 4 mg of Buprenorphine with a repeat of 4 mg on day 1.
    - Day 2 this might be 8 plus 4 plus 4, with further titration up on subsequent days if needed.
  - Works best for methadone doses less than 40 and least well if over 60.
  - Surprisingly, there was a trend for more successful transfer completion when buprenorphine was given in first 24 hours when only mild withdrawal and better transfer when starting doses were less than 4mg.

Different ways to microdose during an induction.

- There are many regimens out there now-not widely validated yet, but the principles are all the same. Buprenorphine gradually takes over the Mu receptors and eventually saturates them with little or none of the original opioid being bound.
- You can taper the full agonist while you are titrating the buprenorphine upwards or you can wait until you get to your target dose of Buprenorphine and then just stop the original opioid. Usually around day 6.

Bernese Method and methods that led to it

- Divide up Buprenorphine pills into eights or quarters and do slow titration. Like starting with .2 mg q 6 hours.
- An example of a regimen would be:
  - Day 1: ¼ of 2 mg pill
  - Day 2: ¼ of 2 mg pill bid
  - Day 3: ½ of 2 mg pill bid
  - Day 4: 1, 2 mg pill bid
  - Day 5: 1 and ½ of the 2 mg pill bid
  - Day 6: 2 of the 2 mg pill bid. Stop or taper down full agonist after day 6, or you might start taper before that.
  - Afterwards, titrate up to 16 mg as needed, or more if needed.

Slightly different, same principle.

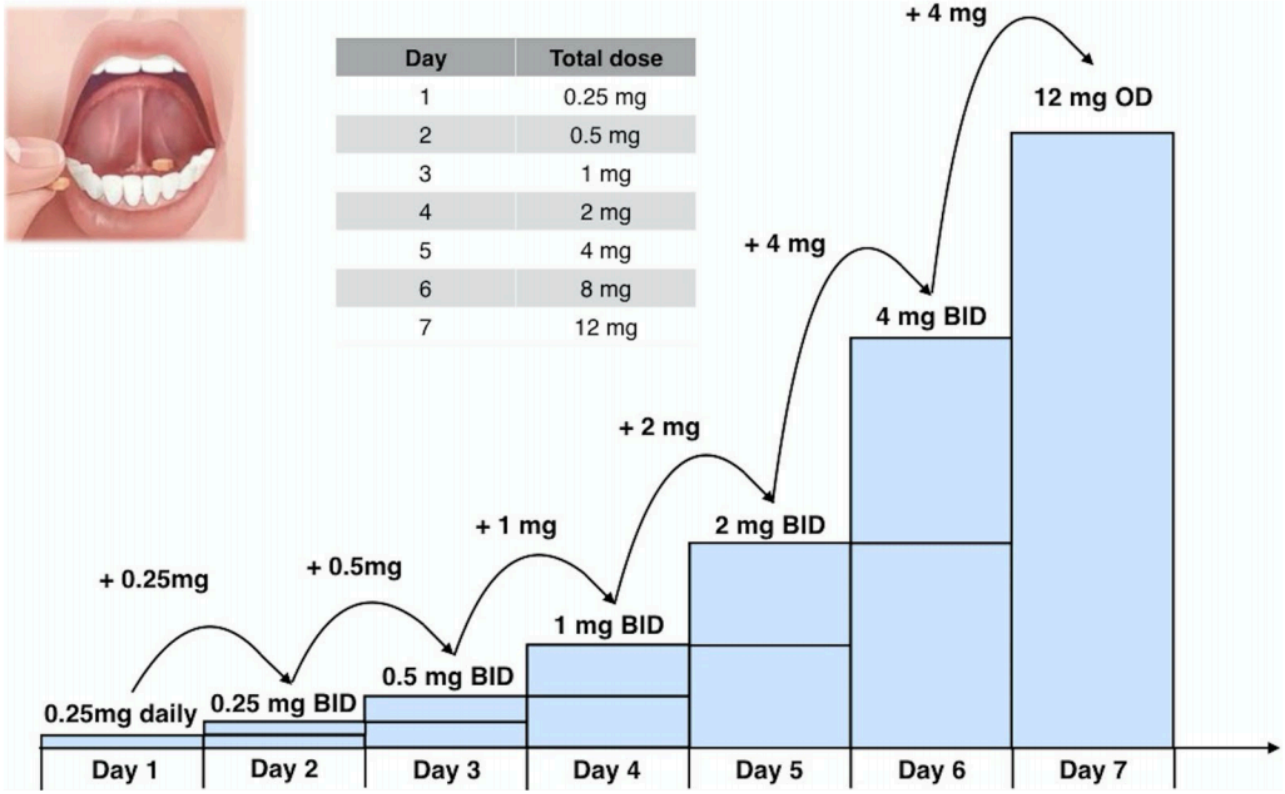

Fig. 1 Buprenorphine/naloxone microdosing regimen (daily witness ingestion). The team partnered with a local pharmacy who were able to split that tablets for microdosing. The tablet splitting may not have been 100% accurate, however it was effective for this patient, given that the technique is to start low and gradually increase and best practice for dosing has yet to be established

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Or a more rapid induction which you might consider for hospitalized patient.

- .5 mg Bup q 3 hours on day 1
- 1 mg q 3 hours on day 2
- 12 mg consolidated dose on day 3 with additional 2 mg prn.

Or over 24 hours

Day 1 time in hours from start of induction	Buprenorphine/Naloxone SL dosing (mg)	Cumulated total dose of buprenorphine over 24 hours	Methadone dose
1	0.5	0.5	50 mg
2	0.75	1.25	–
3	1	2.25	–
4	1	3.25	–
5	1	4.25	–
6	1	5.25	–
7	1	6.25	–
8	1	7.25	–
Day 2	12 and 1–2 mg q3h PRN	12 mg + additional doses	STOP all methadone

SL = sublingual.

24-Hour Rapid Microinduction Dosing Schedule For Buprenorphine/Naloxone SL Using 50 mg of Methadone

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But it can be difficult to break the pills-this is where the transdermal patch or buccal form can help.

- Peak plasma volume from patches occurs at 48 hours.
- Patch 20 mcg = 0.5mg SL daily
- Cost significantly limits this approach

Sample Transdermal regimen

- Day 1: Place 20 mcg bup transdermal patch
- Continue both long and short-acting opioids
- For short-acting, can start SL bup/nlx at 24 hours; for long-acting, wait 48 hours.
- Begin SL dosing with 1 mg BID (1/2 tab).
- Day 2: 1 mg BID
- Day 3: 2 mg BID
- Day 4: 4 mg BID. Once on 8/day, stop or start to taper full agonist or can start taper before this (Heroine)
- Day 5: 6 mg BID
- Day 6: 8 mg BID
- Stop patch a couple of days into it.

Fastest protocol: Lembke & Raheemullah in JAMA March 2019

- Day 1, place 20 mcg bup patch for 24 hours
- Day 2, give 2 mg SL bup/nlx + 2-4 mg prn doses q 2-4 hours for maximum dose of 8 mg.
- Day 3, + 2-4 mg prn doses q 2-4 hours for max dose of 16 mg.
- Remove patch after 48 hours (after day 2). Discontinue full agonists by end of day 3.

Sample Buccal Regimen

- 150 mcg every 6 hours on day 1
- 450 mcg every 6 hours on day two
- 1 mg orally every 6 hours on day 3
- 2 mg orally every 6 hours on day 4 then they stay with 8 mg
- Once the patient is on 8 mg you can try to take off the full mu agonist or leave it on temporarily if they need it for pain.

Many different ways to do this.

- Another regimen uses two 20 mcg patches staggered over 3 days, and then checking for bup in urine 1-2 days after second patch placed. If Bup found in urine, stop full agonists and start induction.
- Or place two 20 mcg patches in first 24 hours, then stop full agonist. If the patient experiences no withdrawal then continue with the modified induction by adding 1 to 2 mg of buprenorphine/naloxone SL every hour until the patient reaches the 12 mg max for day 1 with a subsequent regular titration schedule. If the patient feels some withdrawal then hold the next 1 mg dose until their Clinical Opioid Withdrawal Scale starts to increase, then continue with modified induction as before with 1 to 2 mg titrations every hour until the daily maximum dose is achieved.

Conclusion, pros and cons.

- Can avoid significant withdrawal
- Can avoid significant pain
- Might be more acceptable to patients, especially ones who have failed typical inductions.
- But regimens can seem complicated.
- Can take longer than typical induction.

References

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