MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Microdosing and Extended-Release Buprenorphine

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Why Bother with Microdosing?

- Growing consensus that Bup is standard of care for OUD
  - better safety profile than methadone
    - lower OD risk (esp. as many patients continue to use other sedating substances when on mOUD)
    - fewer medication interactions
    - no concern for QTc prolongation
  - greater ease of access than methadone (esp. in rural communities and residential treatment programs)
- However, **Bup can be difficult to initiate** due to risk for precipitated withdrawal (esp. in patients who have experienced this before)

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019
Marteau, McDonald, and Patel, 2015
Ling, W., Shoptaw, S., and Goodman-Meza, D. (2019).

Problems with Traditional Bup Induction

- **Traditional induction** requires the need for "opioid washout," waiting for moderate opioid withdrawal before starting Bup (12-36 hours, sometimes 96 hours for methadone).
  - This necessary withdrawal period poses **an intolerable barrier to treatment initiation for many**
  - There is *still* risk of worsening withdrawal when Bup is started
  - Further complicated if the patient has chronic or acute pain treated with opioids

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019

Additional Trouble with Fentanyl

- Rapid onset, short duration of action
- Old pharmacokinetic studies relied on single/limited dose administration, resulting in half-life of 1.5 to 7 hours
- However, there are reports of precipitated withdrawal with traditional bup inductions in patients using illicit fentanyl despite patients waiting until they are in moderate to severe withdrawal based on COWS (sometimes waiting over 48 hours)
- Fentanyl is **highly lipophilic**, and so for those chronically exposed to fentanyl we see increased volume of systemic fentanyl distribution and slow dissipation
  - **"mean time to fentanyl clearance from urine was 1 week and norfentanyl clearance was nearly 2 weeks"** (similar to THC)
- **Non-pharmaceutical fentanyl** is complete unknown, ?may be even more lipophilic

Huhn, Hobelmann, Oyler, and Strain, 2020
Randhawa, Brar, and Nolan, 2020
Weimer, M., B., Guerra, M., Morrow, G., Adams, K. (2020).

Basic Concept of Microdosing

1. Continue full mu-receptor agonists (illicit or prescribed)
2. Introduce Bup (with its long half life, high mu-receptor affinity, but only partial mu-receptor agonism) **as slowly and gently as possible**
3. As Bup is slowly increased, the full agonist is slowly displaced by Bup, which mitigates (or eliminates) the potential for precipitated withdrawal
4. Eventually, Bup completely out-competes the full agonist for the mu-receptors and saturates the mu-receptors, at which point the full agonist can be rapidly tapered off or simply discontinued

What About the Full Agonist?

- No need to cross taper down the full agonist during this time
  - Bup slowly out-competes the full agonist, reducing the amount of full agonist that has purchase on the mu receptors, even if full agonist total daily dose remains consistent
  - **Bup slowly "tapers" the full agonist down for you**
  - Still, many protocols recommend reducing full agonist dose as much as tolerated before starting

Multiple Microdosing Protocols

- **Many methods** published in case reports and case series
  - Different timelines
  - Various formulations of Bup (SL, transdermal, buccal, IV)
  - Different patient populations (OUD, chronic pain, inpatient vs outpatient)
  - Some taper full-agonists down to a particular MME prior to starting Bup
  - Some taper full agonist while Bup is titrating up, some keep full agonist at full dose until Bup reaches ~12 mg/day and then simply discontinue the full agonist

The Forerunner: The Bernese Method

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Hammig, Kemter, Strasser, von Bardeleben, Gugger, Walter, . . . Vogel, 2016

Drawbacks of the Bernese method

- Protocol takes at least five days
- Study was done in Switzerland, and 0.2 mg SL Bup formulation is not available in the United States
  - 2 mg dose is smallest available in the US (both film and tab), can quarter it to 0.5 mg

Modified Bernese

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg[a] SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in A.M. and 4 mg SL in P.M.	Full dose
8	12 mg SL/day	Stop

SL = sublingually.

[a]For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Terasaki, Smith, and Calcaterra, 2019

Buccal Bup Microdosing

- Belbuca 225 mcg = 0.5 mg SL Bup
- Basically Bernese method but using Belbuca for first three days avoid cutting any SL strips
- However Belbuca is only FDA-approved for chronic pain

TABLE 2. Buccal Buprenorphine Induction Strategy

Day	Buccal Buprenorphine Film Dose	SL Buprenorphine/Naloxone Film Dose	Full Opioid Agonist Dose
1	225 mcg PO once (75 mcg film + 150 mcg film)		Full dose
2	225 mcg PO twice daily (75 mcg film + 150 mcg film)		Full dose
3	450 mcg PO twice daily		Full dose
4		2 mg SL BID	Full dose
5		4 mg SL BID	Full dose
6		4 mg SL TID	Full dose
7		4 mg SL TID – 8 mg SL BID	Stop

BID, twice daily; PO, per oral; SL, sublingual; TID, 3 times daily.

Weimer, M., B., Guerra, M., Morrow, G., Adams, K. (2020).

“Rapid” Microinduction

- Bernese type protocols dose Bup **Q12H**
- “Rapid” protocols dose Bup at **Q1-4H**
- SL Bup’s time to peak plasma concentration is 60 to 90 minutes, making more frequent dosing feasible

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019
Chiang, and Hawks, 2003

Rapid Microdosing Protocols

TABLE 1. Titration schedule for Case 1

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

TABLE 2. Titration schedule for Case 2

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

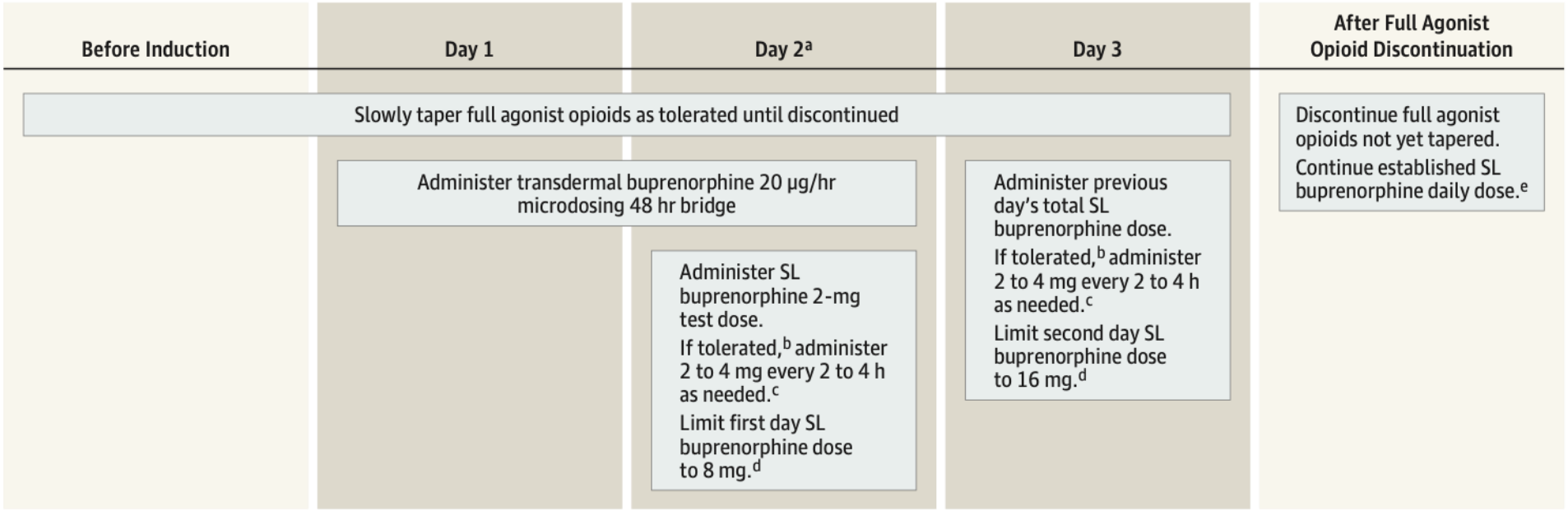
Klaire, Zivanovic, Barbic, Sandhu, Mathew, Azar, 2019

Rapid Microdosing Protocol Used at MGH

DAY	TOTAL DAILY DOSE	HOW TO TAKE	HOW TO TAKE (2-0.5 mg SL films)	METHADONE (OR FULL AGONIST) DOSE
1	4 mg	0.5 mg Q3H x8 doses	1 quarter film Q3H x8 doses	Full dose
2	8 mg	1 mg Q3H x8 doses	2 quarter films Q3H x8 doses	Full dose
3	12 mg to 16 mg	12 mg in AM and 2 mg q2h x2 PRN withdrawal/cravings	8-2 mg SL film and a 4 mg SL film in the morning, 2 mg SL film in evening PRN	Discontinue

Transdermal Bup, several methods

Figure. Buprenorphine Induction With Transdermal Buprenorphine Microdosing



Raheemullah and Lembke, 2019

Transdermal Bup, two more methods

Method 1:
Day 1: Apply 40mcg of transdermal buprenorphine (approx 1mg) for 6 days.
Day 4: As methadone dose >60, recommend reduce dose to 30-40mg day 4
Day 7:
-Administer 1mg SL buprenorphine/naloxone test dose, observe two hours.
-If withdrawal symptoms emerge/COWS increase, hold further doses until COWS returns to base
-If COWS remains the same or decrease, administer 1-2mg SL buprenorphine. Observe 2 hours.
-Repeat to a maximum of 12mg buprenorphine SL
Day 8: maximum 16mg
Day 9: 20-24mg

Method 2:
Day 1: 20mcg patch x1
Day 3: apply 20mcg patch x2; decrease methadone dose
Day 5: apply 20mcg patch x3; decrease methadone dose
Day 7: Stop methadone, continue increasing bup dose with SL Bup as tolerated

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019

Transdermal Bup Considerations

- Designed as a 7 day patch for **chronic pain**
- Patch reaches peak plasma concentrations at 48 hours
- 20 mcg/hour patch —> 480 mcg/day —> roughly 0.5 mg Bup at 24 hour mark
- Patches are expensive, typically not on hospital formulary, and when used outpatient require diagnosis of chronic pain in order for insurance coverage

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019
Raheemullah and Lembke, 2019

Other methods not covered here

- “Azar method” using transdermal fentanyl patch
- Slow-release oral morphine (SROM) methods
- Both involved converting daily opioid requirement/use to equipotent dose of a more predictable a short acting full agonist like fentanyl patch or SROM, then maintaining on this opioid to achieve washout of previous opioids, then using a traditional SL Bup induction
- IV Bup microdosing has also been reported

Ghosh, Klaire, Tanguagey, Manek, Azar, 2019

CAUTION with Microdosing

- **Data is limited** to case reports and case series
- There are **no randomized trials** directly comparing ANY microdosing protocol to traditional Bup induction (or to other microdosing protocols) for tolerability, treatment retention, etc.
- Off label use of medications
- Collaborating with methadone clinics on microdosing in outpatient setting has been challenging
- **HOWEVER**: Benefits likely outweigh the massive risk of patient with OUD going without standard of care and lifesaving treatment with Bup maintenance

Terasaki, Smith, and Calcaterra, 2019

Final Recommendations for Microdosing

- Any microdosing protocol can work so long as it adheres to basic principles of small doses increased stepwise while patient is maintained on full agonist opioids
- Ok to be **flexible** if patient skips or delays a dose
- Use **comfort medications aggressively**
  - clonidine, acetaminophen/ibuprofen, Bentyl, consider a benzodiazepine
- A strong **therapeutic alliance** with patient (esp. with OUD patients) is key, as many are traumatized by previous precipitated withdrawal
- Daily phone call check-ins if outpatient
- Education and direct involvement of hospital/community **pharmacists** and of **bedside nursing**
- Create **order sets** to simplify protocols

Long Acting Buprenorphine - Why?

- SL Bup is new standard of care, but it has drawbacks:
  - **potential for withdrawal** if missed/forgotten dose/loss of access due to insurance or pharmacy issue
  - patients must remember to take regularly
  - **stigma** of being seen with SL Bup
  - illegal to carry doses without the entire Rx bottle
  - misuse/diversion/unintended use/accidental poisoning
  - concern for diversion in correctional settings limits access
  - patients with **housing instability** may have issues storing Bup safely and securing it from theft
  - **SL Bup can have inter-dose fluctuation in plasma concentration, which could cause daily swings in receptor occupancy, leading to instability/cravings/use**
- Goal: provide sustained buprenorphine exposure throughout an extended dosing interval, at concentrations sufficient to control all aspects of the disease (craving, withdrawal symptoms, and **blockade** of other opioids)

Ling, Shoptaw, and Goodman-Meza, 2019

Bup implant: Sixmo®/Probuphine®

- Six-month-long implant (4 implants) to upper arm, max of two successive doses
- Provides consistent serum levels over 6 months
- **For patients previously treated with max dose 8 mg SL Bup and stable for three months (!)**
- Surgical placement/removal requires local anesthesia and special in-person provider training
- No concerning safety issues in trials
- Double blind randomized placebo-controlled trials showed similar efficacy compared to SL Bup

Chappuy, Trojak, Nubukpo, Bachellier, Bendimerad, Brousse, and Rolland, 2020
Ling, Shoptaw, and Goodman-Meza, 2019

Injectable Extended Release Bup: Sublocade®

- One-month long depot injection, immediately turns into a solid, no special training required, RN can administer
- Two dose schemes: 300 mg (1.5 mL) and 100 mg (0.5 mL)
  - 300 mg loading for first two months, followed by maintenance period of monthly 100 mg maintenance
  - Some patients with severest OUD have been maintained at 300 mg Qmonth
- Patient must be maintained on SL Bup > 8mg, for > 7 days prior to injection
- Sub-cutaneous injection to abdomen only, can be painful, pre-medication with local lidocaine (1-3 cc) is MGH standard. Ice pack also helpful.
- Must be stored refrigerated and highly secure as diversion and IV use could result in thromboembolic events
- Initial studies did not compare it directly to SL Bup
- Some retrospective data to support treatment retention is greater with Sublocade vs SL Bup

Chappuy, Trojak, Nubukpo, Bachellier, Bendimerad, Brousse, and Rolland, 2020
Jones, Ngaimisi, Gopalakrishnan, Young, Laffont, 2020
Rioux, Cuellar, Oliver, Hsu, and Szapkiw, 2020

Brief Sublocade® Pharmacokinetics

- Sublocade was designed to deliver a level of plasma buprenorphine that translates into at least a 70% sustained mu-opioid receptor occupancy in the brain over 1 month
  - after second injection, could block “drug-liking” effects of hydromorphone at 6 and 18 mg IM
- Half life is 43 to 60 days, takes 4-6 months to steady state
- Predicted that 2-week occasional delay in dosing would not impact efficacy
- May test positive for Bup months after last injection
- Hope that it will “auto-taper” for patients wishing to discontinue Bup, but this has not been studied

Ling, Shoptaw, and Goodman-Meza, 2019

Injectable Extended Release Bup: Brixadi®

- Week-long or month-long subcutaneous depot injection
  - **Weekly** dosages 8, 16, 24, or 32 mg (volume between 0.16 and 0.64 mL)
  - **Monthly** dosages 64, 96, 128, or 160 mg (volume between 0.18 and 0.36 mL)
  - dose does not correspond linearly to SL Bup doses, need to use chart
- Stored at ambient temperature, no special training required, administered to buttock, leg, arm, or abdomen, immediately turns into a liquid-crystalline gel
- Can start for people not currently maintained on SL Bup
- Safety profile similar to SL Bup with exception of injection site reactions (in greater than 5%)
- Double-blind RCT found it comparable to SL Bup for people not treated with SL Bup in the past 60 days
- Higher weekly doses shown to block hydromorphone IM

Chappuy, Trojak, Nubukpo, Bachellier, Bendimerad, Brousse, and Rolland, 2020
Ling, Shoptaw, and Goodman-Meza, 2019
Soyka, 2020

Long Acting Bup - Final Thoughts

- **Not a panacea**, but another helpful tool
- Although efficacy in clinical trials has been proven, **there is no demonstrated superiority of long-acting Bup over daily SL Bup**
- Safety data are reassuring, adverse effects are mild (similar to SL Bup)
- Reduce number of required clinic visits, eliminate need for take home meds, reduce stigma associated with frequent SUDs clinic vis and having mOUD at home or on person, allow patients to travel freely
- **Reduce pre-occupation with meds** that many SUDs patients suffer

Ling, Shoptaw, and Goodman-Meza, 2019

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