ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Agenda

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Session Date: Friday, April 16, 2021

Didactic Topic and Presenter:
Microdosing as an Approach to Buprenorphine Initiation

Randall Brown, MD, PhD, DFASAM
Associate Professor, Dept. of Family Medicine & Community Health
UW School of Medicine and Public Health
Director, UW Addiction Medicine Fellowship Program
Content Experts:
Ritu Bhatnagar, MD; Lindsey Peterson, MS, CRC; Sheila M. Weix, MSN, RN, CARN

- 12:15 PM: Attendance text-in – Introductions
- 12:25 PM: Didactic Presentation
  - Presenter: Randall Brown, MD, PhD, DFASAM
- 12:40 PM: Case Presentation
  - Presenter: Rebecca Kellum, MD
- 1:15 PM: End of Session

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Interprofessional Continuing Education Partnership
UNIVERSITY OF WISCONSIN-MADISON
School of Medicine and Public Health
School of Nursing
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Project ECHO
University of Wisconsin

ECHO ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics
2020-2022
Microdosing as an Approach to Buprenorphine Initiation
4/16/2021

Didactic Presenter: Randall Brown, MD, PhD, DFASAM
Case Presenter: Rebecca Kellum, MD

Provided by the University of Wisconsin–Madison Interprofessional Continuing Education Partnership (ICEP)

Intended Audience:
Nurses, Nurse Practitioners, Pharmacists, Physicians, Physician Assistants, Pharmacy Technicians, Psychologists, Social Workers, Patient/Caregivers, Students

Objectives:
As a result of this educational regularly scheduled series, learners as members of the healthcare team will be able to:

1) Explain pharmacological rationale for considering microdosing as an approach to initiating buprenorphine for OUD
2) Discuss existing literature surrounding microdosing

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Name	Role	Financial Relationship Disclosures	Discussion of Unlabeled/Unapproved uses of drugs/devices in presentation?	COI completio date
Randall Brown	RSS Chair	No relevant financial relationships to disclose	Yes	3/11/21
Nada Rashid	RSS Coordinator	No relevant financial relationships to disclose	No	3/11/21
Kathleen Maher	Planner	No relevant financial relationships to disclose	No	3/15/21
Ritu Bhatnagar	Planner	No relevant financial relationships to disclose	Yes	3/12/21
Paul Hutson	Planner	No relevant financial relationships to disclose	Yes	3/11/21
Susan Mindock	Planner	No relevant financial relationships to disclose	No	3/11/21
Lindsey Peterson	Planner	No relevant financial relationships to disclose	No	3/11/21
Sheila Weix	Planner	No relevant financial relationships to disclose	No	3/11/21
Randall Brown, MD, PhD, DFASAM	Presenter	No relevant financial relationships to disclose	Yes	4/1/21
Rebecca Kellum, MD	Presenter	No relevant financial relationships to disclose	No	3/25/21

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ACCEPT

Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Patient Case Presentation

***Please do not attach any patient-specific files or include any Protected Health Information.**

1. Date: 4/16/21
2. Presenter Name: Rebecca Kellum, MD
3. Presenter Organization: UW Addiction Medicine Fellowship
4. ECHO ID: 1786
5. Have you presented this patient during this teleECHO clinic before? ☐ Yes x No

6. Please state your main question for this case:
   - **call to Addiction Medicine consult line: pt on methadone 145mg who wants to stop abruptly so she can move to a more stable living situation in another city (job, family support, proximity to her children). Asking if she can resume bup/nlx (had been on 16mg/d until 4 months prior when she returned to use and switched to methadone).**

Patient Demographic Information:

7. Age: 30
8. Gender: cis-female
9. Education/Literacy:
10. Income source:
11. Social Factors/History:

12. **Substance Use History:**
    - started using oxycontin at age 18 after being given pain medications for infected wisdom teeth. She was going through trauma at the time and liked how they helped that pain. She started using heroin at age 22, initially just inhaled and later injecting.
    - intermittent use of benzodiazepines, cocaine, alcohol.
    - in her early 20s, was in a relationship with a man who was physically abusive to her, would "hold drugs over her." Would have her steal credit cards and send her to buy gift cards with them. The father of her 10 year-old daughter "got her out of that."
    - 2012: had been on and off methadone before. OD x2. Then receiving methadone through local clinic, but it closed due to licensure issues. Switched to a different methadone clinic but insurance no longer covering travel there and it costs $300 per trip. Pt planning to taper of methadone due to difficulty in travelling. Pt requesting

alprazolam rx for anxiety; not prescribed due to risks. Taper also interrupted by 3 days in jail. Later went to ED for w/d with fast methadone taper. Pt reportedly angry and left because they "wouldn't prescribe long-acting narcotic to treat non-life threatening opiate withdrawal."

- 2017 residential treatment after incarceration x1 year. Resumed bupropion for depression, anxiety and panic attacks. Also sleep-onset insomnia.
- 11/2018 admitted for overdose. Friends drove her to ED after she overdosed on "oxy." Had recently resumed use after stopping for a while. Accidental overdose. UDS positive for bzd and opioids.
- was at an addiction treatment center IOP 6/2019 - 1/2020 and then left for maternity leave. Was not on MOUD while pregnant and felt motivated by her pregnancy to remain off opioids. Reports developing post-partum depression and returning to heroin use 2/2020. Only inhaled, about $50 per day. Pt requested bup/nlx. Had been on vivitrol before and didn't find it helpful for cravings.
- home induction through my clinic 3/2020. Pt and her husband living in apartment across the hall from patient's mother, who was caring for her 2 month-old baby while she had returned to use. Both husband and mother supported pt's recovery. Pt was able to see her child every day. Had plans to resume 4 day/wk addiction treatment center IOP. Stabilized on 16mg/d.
- Soon after 8/20 right carpal tunnel release surgery, she had a return to use. Tried to resume the bup/nlx she had at home and underwent precipitated withdrawal. Established at local OTP for methadone treatment. Continued some heroin use initially, but then did well, eventually on 145mg/d.
- she notes that during this period, she was still focused on not losing her son. Was paying her bills. Would only use when her son was with his dad. Would "stop right away, when I relapsed." Was honest with her kid's dad because she didn't want him taking him away.
- **12/2020: called my office to ask about getting back on suboxone. Her father is willing to help her by getting her a job, getting her a car and a place to live close to him. Her children are living with her dad and she would be able to see them regularly. The job starts in two weeks -- she felt she must take the chance because her father's wife was able to get her a job locally despite the pt's felony conviction. She was on methadone 145mg but was going to stop abruptly so she could move close to father.**

13. <u>Consequences of Substance Use:</u>

- Social/occupational/educational:
  - children in custody of her father.
  - felony charge limited access to employment

- Physical (including evidence of tolerance/withdrawal):

- 2017 treated for scabies while living in halfway house post-incarceration
- 11/2018 admitted after overdose, and apnea, reversed with narcan in ED.
- 12/2018 ED treatment for multiple skin abscesses
- HCV (began treatment 2/2021)

14. <u>Interventions that have been tried:</u>

- prior vivitrol: pt didn't find it helpful with cravings
- bup/nlx started 3/2020
- methadone started 8/2020

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15.

Current Addiction and Mental Health-related Medications:	Medical/Behavioral Health Diagnosis:
● buproprion 150mg/d ● mirtazapine 15mg ● nicotine gum	● depression ● post-partum depression ● anxiety ● HCV (on mavyret)

16.

Patient Strengths/protective factors:	Risk factors:
● multiple prior self-initiated attempts to stop heroin use ● motivated to regain custody of her children ● motivated to have employment ● family support (housing, car, link to employment). improved relationship with her father and brother. Father also supportive of pt engaging in positive interactions with her son's dad ● would only use when her infant son was with his dad.	● precarious living situation. ● not connected to counseling or psychiatric treatment yet ● feels at higher risk for heroin use in current location. "only knows users here." wants to move close to father in different city, but treatment options there more limited. ● insurance change after becoming employed (off medicaid) ● felony conviction in her 20s

17. <u>Labs (as indicated), include summary of urine testing or last urine drug screen results:</u>

ALT/AST: max 5/2019 287/147 (5 xULN)

HCV RNA quant: 2/2021 10 million → 3/21 146

18. <u>Patient Goals/Motivations for Treatment:</u>

- didn't "want to make any mistakes that would keep her from getting her son back." Her father had adopted her daughter (now 10 yo).
- find work
- get out of current location where she struggled not getting back into the same routine. was using heroin when on methadone.
- treat her HCV

19. <u>Proposed Diagnoses:</u>

OUD, severe

depression, anxiety, panic

possible PTSD

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20. <u>Proposed Treatment Plan:</u>

- micro-induction protocol per Dr Brown. Home induction.

day #	date	day of the week	bup dose (2mg strips)	metha-done dose	communication/visits
#1	12/30	Wed	0.5mg (¼ strip)	145mg	call: going well. not sick
#2	12/31	Thurs	1 mg (½ stip)	145mg	
#3	1/1	Fri	2mg (½ strip twice that day)	145mg	call: mild w/d. going well.
#4	1/2	Sat	3mg (½ strip three times)	145mg	
#5	1/3	Sun	4mg (1 strip twice that day)	145mg	son's 1st birthday party
#6	1/4	Mon	6mg (1 strip three times)	145mg	I spoke with methadone provider, who had been out of town. OV: runny nose, hot/cold flashes -- mild w/d. clonidine helping. adjusted protocol to stop methadone on day #9 instead of day #8. add 12mg/d on day #8
#7	1/5	Tues	8mg (2 strips twice that day)	145mg	
#8	1/6	Wed	16mg → 12mg/d	STOP → 145mg	
#9	1/7	Thurs	16mg/d	STOP	call: feels fine.
#10	1/8		16mg/d	d#2 w/o mthdn	call: still good. no w/d.
#11	1/9		16mg/d → 24mg/d	d#3 w/o mthdn	call: increased w/d. plan to increase to 20-24mg/d if needed.
#12	1/10...		24mg/d	d#4 wo mthdn	call: took third 8mg strip night before.
#15	...1/13		24mg/d	d#7 wo mthdn	OV: mild w/d. trouble sleeping, a new s/d sx for her. will take third strip earlier in the day

1/21 OV: mild withdrawal, but now having trouble sleeping with it, something she hadn't had before. will take her third strip earlier in the day. Met with her counselor at methadone clinic that day. Starts work next week.

1/21 call: check-in: doing great on 24mg/d. Started working second shift, which is great because it gives her time to take her son to daycare before work. Requesting to change the time she meets with me next week.

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2/21: things are going really well. Still has a hard time sleeping. Wonders if it is due to coming of methadone. Plan to switch from bupropion to sertraline and start mirtazapine.

3/21 call: didn't feel right after stopping bupropion, so stayed on it.

4/21: called to say she has new insurance from her job and needs to see someone at a different hospital system. I will refill bup/nlx until she can establish. I communicated with Allison Miller, whose office will reach out to patient for scheduling.

By initialing here ___RIK____ you have acknowledged that Project ECHO case consultations do not create or otherwise establish a provider-patient relationship between any ECHO clinician and any patient whose case is being presented in a teleECHO clinic.

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Microdosing as Approach to Buprenorphine Initiation

Randall Brown
UW ECHO ACCEPT
April 16, 2021

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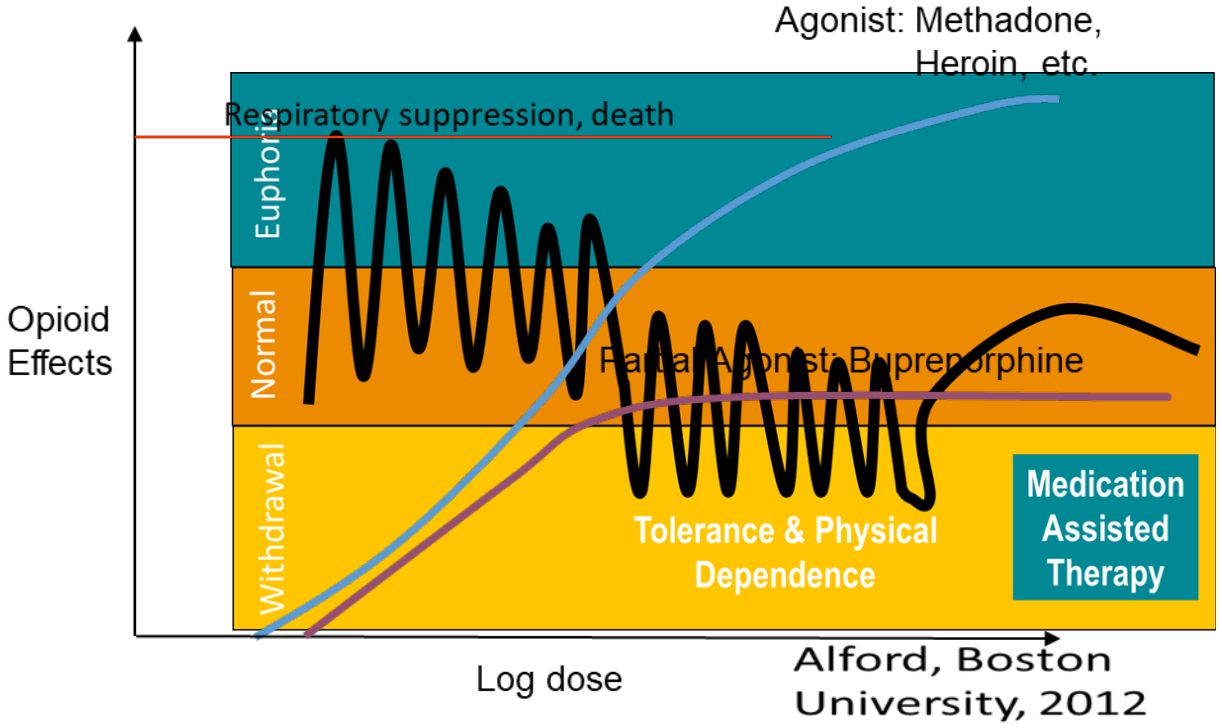
Buprenorphine for Opioid Use Disorder

- Partial opioid agonist w/ high μ-opioid receptor affinity & slow dissociation kinetics
- Long $t_{1/2}$ (26-37 hours)



Importance

- Partial agonist + high μ-opioid receptor affinity → buprenorphine may precipitate withdrawal in people physically dependent on full opioid
- May complicate transition from long-acting opioid
  - Methadone
  - Chronic fentanyl
- Complicated initiation/prolonged withdrawal symptoms ↓ likelihood of treatment engagement and retention

Conventional Transition from Methadone

- Taper to 30-40mg
- Stable on this dose x 7 days
- Buprenorphine initiation at 36-72 hours out from last dose
  - Can take weeks or months
  - Potential destabilization & OD risk as dose decreases & during abstinent window
  - Requires close monitoring and careful coordination at/with OTP

Fentanyl & Analogs

- ↑↑ presence in illicit supply
- Available literature re: pharmacodynamics pertains to commercially produced fentanyl
- High potency, highly lipophilic
  - → protracted excretion patterns
  - Urine testing may be positive days after last use
  - Extended μ-opioid receptor effects
  - ↑ risk for precipitated w/d w/ conventional initiation

Some Underpinnings of Microdosing

- Repetitive naloxone administration → max w/d Sx sooner that later decline despite ongoing admin
- 0.2mg IV buprenorphine did not → precipitated w/d
- So. . .
  - Repeated, adequately spaced (e.g. 12 hr) bupe may not ppt w/d
  - Slow bupe dissociation → gradual accumulation at μ receptors w/ repeated dosings
  - Over time, ↑ amt of full opioid replaced by bupe at μ receptors

Resnick et al, 1977. Clin Pharm Therapeutics
Mendelson et al, 1997. Biol Psychiatry

Case Series': Microdosing Initiation

- 3 hospitalized patients w/ OUD
- Daily methadone 40-100mg
  - 2 pt initiated on methadone during hospitalization
  - All were using illicit opioid prior to admission (use duration 2-10+ yr)
- All had co-morbid painful condition

Terasaki et al, 2016. PharmacoTx.

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

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.

Case Series': Microdosing Initiation

- 2 patients
  - 1 – prior initiation w/ withdrawal and "trauma reactivation" during conventional initiation
  - 2 – maintained on high doses of methadone + diacetylmorphine (heroin)

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

Hammig et al, 2016. Subst Abuse Rehabil.

Also see. . .

- De Aquino et al, 2020. J Addiction Med.
- Martin L et al, 2019. Canadian J Addiction.
- Klaire et al, 2019. Am J Addictions.
- Brar et al, 2020. Drug Alc Review.
- Rozylo et al, 2020. Addiction Sci & Clin Practice.
- Moe et al 2020. Addictive Beh.
  - Systematic review—19 case studies, 56 patients, 26 different regimens
  - All patients achieved desired maintenance dose

Considerations for practice

- When to microdose (or offer it)?
- Alternative practices prior to initiation?
- Observed vs unobserved initiation?
- Urine testing modalities and work flow?

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