



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

**USING & INTERPRETING URINE
BUPRENORPHINE & NORBUPRENORPHINE
LEVELS
+ A PRIMER ON BUPE ‘MICRODOSING’
INDUCTIONS**

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GENERAL DISCLOSURES

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

No conflicts of interest, including no financial conflicts of interest with any manufacturers of any medications mentioned here

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose:

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LAND ACKNOWLEDGEMENT

- As we begin our talk, I respectfully acknowledge that our event today (where I am) is taking place on occupied Coast Salish land on the homelands of the Duwamish people.
- I pay respect to Coast Salish Elders past and present and extend that respect to their descendants and to all Indigenous people.
- To acknowledge this land is to recognize its longer history and our place in that history.

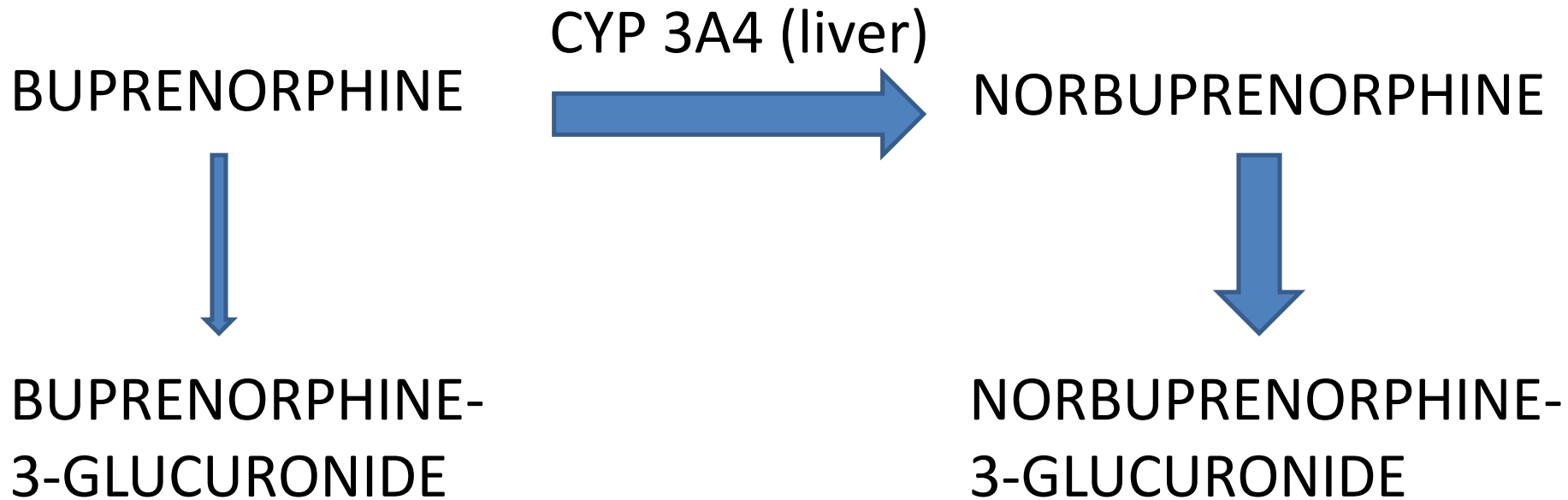
OBJECTIVES

1. Explain how quantitative urine buprenorphine & norbuprenorphine levels might add clinical value
2. Interpret urine bupe & norbupe levels and use that information in a therapeutic – not punitive - manner
3. Use a buprenorphine ‘microdosing’ approach for a patient who struggles with a standard outpatient induction

BUPRENORPHINE METABOLISM

- Extensive 1st-pass metabolism = SL or buccal use (or implant or subcutaneous depot)
- Rapid SL/buccal absorption (peak ~0.5-3.5 hrs)
- Bupe via CYP3A4 → norbupe (active metabolite)
- Most bupe/norbupe excreted in feces
 - 10-30% via urine, detectable for 2-4 days, or longer*

BUPRENORPHINE METABOLISM



Drugs/conditions that inhibit or induce CYP 3A4, and genetic polymorphisms that affect CYP 3A4, can diminish or enhance bupe metabolism

Concurrent HCV increases bupe & norbupe levels

= Individual variation in metabolism occurs

OFFICE-BASED BUPE CARE

- For reasons of respect for patients, de-stigmatizing OUD, and efficiency:
 - Dosing is rarely monitored
 - Urine samples rarely, if ever, provided under supervision
- May result in:
 - Poor technique = poor absorption
 - Variable dosing
 - Submerging of bupe into a urine sample

OFFICE URINE TOXICOLOGY

- Point-of-care immunoassays common
- Urine specimen integrity assessment:
 - Temperature, pH, specific gravity, creatinine, nitrites
- Submerging of bupe film/tablet in urine maintains urine integrity, causes positive immunoassay
- Confirmatory testing via lab send-offs (GCMS vs LCMS)

LITERATURE ON URINE BUPE, NORBUPE LEVELS

- ↑ SL/buccal doses = ↑ plasma & creatinine-normalized urine levels
 - Wide inter-subject variability = cannot use levels to determine dose taken
 - Urine bupe often > 20 ng/mL*
 - Urine norbupe often > 45 ng/mL*
- Bupe:norbupe ratio
 - No association with dose
 - Often < 1 (median ~ 0.23)
 - Wide inter-subject variability
 - Dependent on timing of last dose

* Single small study (N=46), 2-18 mg bupe daily

LITERATURE ON URINE BUPE, NORBUPE LEVELS

- No apparent association between levels or ratio and whether urine was positive or negative for non-prescribed opioids
- Suggestive of “dipping”
 - Urine bupe:norbupe > 3.85
 - Urine bupe level > 700 ng/mL
- Urine naloxone > 200 ng/mL suggestive of parental use of bupe-naloxone

CASE 1

- 20ish year old
- Rx'd 16 mg buprenorphine-naloxone daily
- Engaged in care, lower heroin use reported
- Point-of-care immunoassay = bupe positive
- Lab confirmation:
 - Buprenorphine >1500 ng/mL
 - Norbuprenorphine = 123 ng/mL

Differential?

CASE 1: DIPPING & TAKING SL BUPE

Buprenorphine >1500 ng/mL

Norbuprenorphine = 123 ng/mL

- Consistent with dipping bupe into urine
- Consistent also with taking buprenorphine

Client reported taking ~10 x 8 mg films per week instead of the 14. Skipped days to use heroin. Wanted to 'ensure' UDS was positive for bupe.

- MI, emphasize harm reduction, safe space
- rx'd 10 x 8 mg films per week
- Relationship improved, no further dipping

CASE 2

- 30ish year old
- Rx'd 16 mg buprenorphine-naloxone daily
- Newly started, ongoing heroin use reported
- Point-of-care immunoassay = bupe positive
- Lab confirmation:
 - Buprenorphine >1500 ng/mL
 - Norbuprenorphine = negative

Differential?

CASE 2: DIPPING

Buprenorphine >1500 ng/mL

Norbuprenorphine = negative

- Consistent with dipping bupe into urine
- Consistent with no dosing in days prior to visit

Client reported ambivalence about starting, but providing the Rx'd bupe to his partner

→ MI for him, outreach for his partner, emphasize clinic willingness to help both

→ Client opted to try methadone. Partner engaged in care. Client continued primary care services

CASE 3

- 20ish year old
- Rx'd 20 mg buprenorphine-naloxone daily
- Variably engaged, hopes to travel to see family, ongoing heroin use reported
- Point-of-care immunoassay = bupe positive
- Lab confirmation:
 - Buprenorphine 20 ng/mL
 - Norbuprenorphine 25 ng/mL

Differential?

CASE 3: UNDER-DOSING

Buprenorphine 20 ng/mL

Norbuprenorphine 25 ng/mL

- Suggestive of either dilute urine, increased time since last dose, taking lower dose or poor absorption

Client reported a worry about ‘becoming addicted’ to bupe and worry about bupe supply if travels to see family = under-dosing & saving

→ education re: his worry, plans re: his travel goals

→ Led to better adherence, no heroin for periods of time

CASE 4

- 30ish year old
- Rx'd 24 mg buprenorphine-naloxone daily
- Highly engaged, keeping appointments, goal = abstinence, yet struggles with cravings & still uses heroin
- Point-of-care immunoassay = bupe positive
- Lab confirmation:
 - Buprenorphine 31 ng/mL
 - Norbuprenorphine 43 ng/mL

Differential?

CASE 4: POOR ABSORPTION

Buprenorphine 31 ng/mL

Norbuprenorphine 43 ng/mL

- Suggestive of either dilute urine, increased time since last dose (low levels), taking lower dose or poor absorption

Client reported notable dislike of and nausea from SL bupe, would swallow the bupe film “clump” after ~1-2 min

- education absorption & technique; rx'd anti-nausea
- Less cravings, little to no heroin, norbupe later ~700 ng/mL

CASE 5

- 50ish year old
- Rx'd 24 mg buprenorphine-naloxone daily
- Engaged long-term (>1yr), keeping appointments, UDS at times has opiates (and always bupe)
- Point-of-care immunoassay = bupe positive
- Lab confirmation:
 - Buprenorphine 345 ng/mL
 - Norbuprenorphine >1500 ng/mL

Differential?

CASE 5: TAKING BUPE AS RX'D

Buprenorphine 345 ng/mL

Norbuprenorphine >1500 ng/mL

– Consistent with regular adherence in days leading up to urine drug screen

Client reported regular use of bupe as rx'd, rarely missing days. Smokes meth and heroin when offered to him – happens not infrequently in his milieu. Objective improvements on bupe

→MI, discussed ways to intensify treatment

→Pt content with treatment as-is. All norbupe levels have been c/w regular adherence

“PREVENTIVE” STRATEGIES

- Ask up front, at 1st visit and periodically, that patients not ‘dip’ bupe into urine samples
- Create a psychologically safe space. “We’re here to help. Let me know if you haven’t been taking your bupe”
- Review sublingual/buccal technique

KEY POINTS

- Quantitative urine bupe & norbupe levels can give confidence to office-based clinical team & patient that bupe is taken & absorbed
- Sending periodically (at start, & q 3-12 months) may be useful
- Be transparent with urine screens
- Use results to strengthen therapeutic relationship. Retention = better outcomes
- Preventive strategies has reduced 'dipping' for our team

BUPE 'MICRODOSING' INDUCTIONS

- Standard/traditional induction

- Wait til moderate withdrawal (~18-24 hrs)
- Start bupe ~4 mg, increase q 2hrs or so

= Quicker start, but can be uncomfortable withdrawal process, risk of precipitated withdrawal

BUPE 'MICRODOSING' INDUCTIONS

- 'Microdosing' induction
 - Don't stop the full-agonist (eg heroin)*
 - Introduce 'microdoses' (0.25-0.5 mg), gradually increase over 5-7 days
- = Slower start, but can avoid the need to go through a withdrawal phase, lower risk of precipitated withdrawal

*Extra caution / seek consult if pt using methadone

BUPE 'MICRODOSING' INDUCTIONS

- Consider for the person who...
 - Expresses notable fear of the withdrawal process
 - Or... Reports history of precipitated withdrawal, especially with multiple attempts
 - Or... smokes heroin, with compulsions to smoke at frequent intervals (eg q 3-4 hours)
 - And... is organized / good with instructions
 - And... has access to a 5-7 day supply of full agonist opioid (eg heroin)

BUPE 'MICRODOSING' INSTRUCTIONS

- Patients can continue using heroin during this process as they feel the need to
- (Rx the 2mg buprenorphine-naloxone films)
- Day 1: 1/8 of a 2 mg film BID* (0.5 mg total)
- Day 2: 1/4 of 2mg film BID (1 mg total)
- Day 3: 1/2 of 2mg film BID (2 mg total)
- Day 4: 1/2 of 2mg film TID (3 mg total)
- Day 5: 2 mg film BID (4 mg total)
- Day 6: 2 mg film TID (6 mg total)
- Day 7: 4 mg TID + (12+ mg total)

(Can likely skip to day 2 if pt can wait ~4-8 hours after last heroin use)

CASE: BUPE MICRODOSING

- 50ish year old
- Heroin IV, history of precipitated withdrawal with bupe inductions, struggles with sx's 8 hours post-heroin use
- Rx'd 16 x 2 mg buprenorphine-naloxone films for 1 week
- Gave instructions as previously noted
- Phone call check-ins in 1st week
- Less heroin use at 2 mg BID
- No cravings, no heroin use at 4 mg TID
- Consolidated to 12 mg daily thereafter

KEY POINTS

- Bupe ‘microdosing’ can ease the path for patients who struggle with ‘standard’ inductions.
- Frequent check-ins help
- Buprenorphine patch (for 2 days before starting sublingual) and bupe monotherapy can further reduce risk of precipitated withdrawal, but have X-waiver/DEA & insurance problems in outpatient settings

QUESTIONS?

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