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CME MOC

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How do I interpret and use quantitative buprenorphine and norbuprenorphine urine levels?

A PATIENT RETURNS to the outpatient clinic for follow-up of buprenorphine treatment of opioid use disorder. Buprenorphine confirmatory testing at the last visit had shown a urine buprenorphine level greater than 2,000 ng/mL and a urine norbuprenorphine of 220 ng/mL. How do I interpret these results, and when should I order quantitative buprenorphine confirmatory testing?

A: GIVEN THE COST, quantitative testing should be ordered thoughtfully, and only when the results would change clinical management.

Confirmatory buprenorphine testing of urine samples can be useful in outpatient settings where buprenorphine dosing is not directly observed, as in most primary care clinics that offer treatment of opioid use disorder (OUD). Such testing can offer advantages beyond point-of-care immunoassays, including providing confidence to the clinical team on buprenorphine dosing and identification of previously unknown or undisclosed barriers to treatment success. Retaining and engaging the patient in effective treatment should remain the ultimate goals of testing.

BUPRENORPHINE METABOLISM AND LABORATORY ASSESSMENT

Because of its extensive first-pass metabolism by the liver if taken orally, buprenorphine is used sublingually, buccally, via a subcutaneous implant, or via depot injection. Buprenorphine is primarily metabolized by hepatic cytochrome P450 3A4 (CYP3A4) to its active metabolite norbuprenorphine. Buprenorphine and norbuprenorphine are eliminated primarily via the biliary system, with 10% to 30% excreted in urine.[1] Drugs or conditions that inhibit or induce CYP3A4 and genetic polymorphisms affecting CYP3A4 can diminish or enhance buprenorphine metabolism.[1]

doi:10.3949/ccjm.89a.21019

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A buprenorphine film or tablet can be dipped in or submerged into a urine sample to alter the result ("urine spiking"). In such cases, common indicators of urine specimen integrity (temperature, pH, specific gravity, creatinine, and nitrites) can still be within normal limits, and the result of a point-of-care immunoassay would be positive for buprenorphine. Confirmatory testing provides quantification of urinary buprenorphine and norbuprenorphine, as well as naloxone if ordered, using gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry. Both buprenorphine and norbuprenorphine can be detected in urine for 2 to 4 days and possibly longer in people who are taking buprenorphine chronically.[2]

Although higher doses of buprenorphine generally result in higher plasma levels and creatinine-normalized urine levels of buprenorphine and norbuprenorphine, there is wide variability between individuals.[2,3]

Given the individual variability of these levels and the variability in the severity of OUD, these quan-

TABLE 1
Interpreting urinary buprenorphine and norbuprenorphine levels

	Total urinary buprenorphine (ng/mL)[a]	Total urinary norbuprenorphine (ng/mL)[a]	N:B ratio[b]	Differential or likely diagnosis
Scenario 1	> 20	> 45	Usually > 0.26	Recent dosing of at least some buprenorphine
Scenario 2	Low, ≤ 20[c]	Low, ≤ 45[c]	Usually > 0.26	Regular recent dosing Dosing at low levels Use of a CYP3A4-inducer Increased time since last dose Dilute urine
Scenario 3	Positive, but low	Negative or very low	< 1 (may be 0)	Recent (within hours) dosing of buprenorphine for first time in days
Scenario 4	High, usually > 700	Negative	0	Buprenorphine spiking and no recent dosing
Scenario 5	High, usually > 700	Positive	< 0.26	Probable buprenorphine spiking, likely recent dosing if norbuprenorphine level is not low Possible regular dosing when N:B ratio > 0.02 but < 0.26

[a]Total urinary levels listed here include the parent compound and the glucoronidated form (eg, total buprenorphine = free buprenorphine + buprenorphine-3-glucoronide) achieved after laboratory hydrolysis.
[b]Some studies suggest using an N:B ratio of 0.02 as a threshold for identifying urine spiked with unconsumed buprenorphine. Using a more sensitive threshold of 0.26 keeps a broader differential.
[c]Some studies consider values < 100 ng/mL to be low.

CYP3A4 = hepatic cytochrome P450 3A4; N:B ratio = ratio of norbuprenorphine to buprenorphine

titative buprenorphine and norbuprenorphine levels have no proven or apparent role in reliably indicating the dose that has been taken recently, nor do they help determine the effective buprenorphine dose. The effective dose remains a clinical decision. However, quantitative test results can provide reassurance that at least some amount is being taken.

HOW TO INTERPRET BUPRENORPHINE CONFIRMATORY TESTING

The buprenorphine level, norbuprenorphine level, and the norbuprenorphine-to-buprenorphine ratio are important when interpreting results.

Table 1 shows patterns of quantitative levels of buprenorphine and norbuprenorphine and associated differential diagnoses for patients taking sublingual or buccal buprenorphine. These values may not apply to patients receiving extended-release injectable or implantable formulations of buprenorphine.

Sample scenarios for interpreting test results

The test results reported in **Table 1** can be interpreted as follows:

- **Scenario 1:** The values tell us that buprenorphine has been taken recently, but we cannot draw conclusions about the amount taken.
- **Scenario 2:** The values are low. While there is no agreed-upon threshold for "low" values, the upper limit of the lowest quartile among several studies was 20 ng/mL for buprenorphine and 45 ng/mL for norbuprenorphine, although other studies have considered less than 100 ng/mL to be low.[2–5] Low values may be consistent with adherence, given individual variation, but it is reasonable in this setting to engage the patient in exploratory discussions related to dosing consistency, sublingual or buccal technique, and medication interactions.
- **Scenario 3:** In general, the ratio of norbuprenorphine to buprenorphine is often greater than 1, but there is significant individual variability. The

ratio appears independent of dose but dependent on the time since the most recent dose, because plasma and urine levels of buprenorphine rise and fall faster than those of norbuprenorphine.[3,6] The pattern of a positive but low urinary buprenorphine and a lower or negative norbuprenorphine can arise with dosing of buprenorphine for the first time in days only hours (often 0.5 to 2 hours) before providing the urine sample.

- **Scenarios 4 and 5:** Burprenorphine levels are high, while norbuprenorphine levels are low or negative. Several studies suggest a ratio of norbuprenorphine to buprenorphine of less than 0.02 as a threshold for identifying urine spiking, based on data outliers.[5,7–9] In another study, with subsequent patient confirmation of urine spiking as a reference, a norbuprenorphine-buprenorphine ratio of 0.26 or less provided maximal sensitivity but low specificity (58%) for urine spiking, while buprenorphine concentrations of 700 ng/mL or greater had a specificity of 85% and sensitivity of 77%.[10] Elevated urine naloxone levels with thresholds of at least 200 ng/mL are often seen with parenteral use of buprenorphine-naloxone or urine spiking with buprenorphine-naloxone.[4,8] When any of these indicators is present, it is reasonable to consider urine spiking and explore this possibility with the patient. Positive levels of norbuprenorphine likely suggest recent dosing of at least some amount, even in the presence of indicators of urine spiking. However, it is unknown whether low levels of norbuprenorphine in cases otherwise suggestive of urine spiking represent recent dosing or spontaneous formation of norbuprenorphine in vitro from high concentrations of unconsumed buprenorphine.

Case example revisited

In the opening case, the buprenorphine level of greater than 700 ng/mL, the positive norbuprenorphine level, and a low norbuprenorphine-to-buprenorphine ratio (0.11) suggest recent dosing of some amount of buprenorphine and the possibility of urine spiking with unconsumed buprenorphine (scenario 5).

MOTIVATIONS FOR URINE SPIKING

Patients may engage in urine spiking for various reasons. They may have missed doses, lost medication, or diverted some or all of their buprenorphine to help others or for financial reasons, and they may fear the perceived consequences of providing a urine sample negative for buprenorphine. Some may be taking their buprenorphine as prescribed but fear consequences of nonprescribed drug use and thus spike a diluted or acquired urine specimen.[7] In one study, patients who provided spiked urine samples had significantly lower treatment retention rates (defined in this study as adherence to the treatment program until data collection ended) after this finding was discussed with them.[5] Given mortality rates with untreated OUD, it is imperative to approach conversations about urine spiking from a place of empathy for the patient, acknowledging that urine spiking may often reflect treatment struggles and the need for more support. Creating a psychologically safe space for patients, inviting the patient to share treatment-related struggles, and transparency about urine testing are components of effective care and, in our experience, may reduce urine spiking. Retaining patients in care and identifying barriers to effective treatment should be the goals of these conversations.

Indicators of urine spiking include high buprenorphine levels and low norbuprenorphine-buprenorphine ratios

THE BOTTOM LINE

Quantitative buprenorphine and norbuprenorphine testing can be useful in outpatient settings where dosing is not observed. It is reasonable to order it once in the first months of buprenorphine treatment and then periodically (eg, every 3 to 6 months) for patients whose OUD is not in remission, while being transparent with the patient about when urine samples are tested. The levels cannot be used to draw conclusions about dosing amounts but may help identify previously unknown or undisclosed barriers to treatment.

Interpreting the results based on the current evidence and acknowledging their limitations, along with an inquisitive, nonjudgmental communication style, can identify barriers to treatment and enhance clinical care in a way that point-of-care immunoassays cannot. ■

Acknowledgment: *We are grateful to Dr. Petrie Rainey of the Department of Laboratory Medicine, University of Washington, Seattle, for the insightful comments on earlier drafts related to laboratory measurements of buprenorphine and norbuprenorphine.*

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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