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Laboratory monitoring for patients on buprenorphine: 10 questions

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How to best use laboratory testing for patients with opioid use disorder

The opioid use disorder (OUD) epidemic is a major public health crisis in the United States.[1] Naltrexone, methadone, and buprenorphine are first-line therapies for OUD and have high success rates.[2] While studies have shown that naltrexone is effective, patients must achieve opioid detoxification and maintain 7 to 10 days of total abstinence to avoid a precipitated opioid withdrawal before it can be prescribed.[3] Methadone does not require detoxification or a period of complete abstinence, but must be prescribed in special clinics and requires daily observed dosing for the first 90 days,[4] though these requirements have been relaxed during the COVID-19 pandemic. In contrast, buprenorphine (with or without naloxone) can be used in office-based settings, which significantly improves the accessibility and availability of treatment for patients with OUD. Clinician knowledge and comfort prescribing buprenorphine are limiting factors to treatment.[5] Increasing the number of clinicians proficient with buprenorphine management can improve access to effective treatment and recovery services, which is critical for patients with OUD.

Multiple resources are available for clinicians to learn how to prescribe buprenorphine, but clear guidance on laboratory testing for patients receiving buprenorphine is limited. To safely and effectively prescribe buprenorphine,

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clinicians need to understand its pharmacology (***Box 1,***[6-9] ***page 14***) and how laboratory testing influences treatment. In an effort to increase clinician knowledge of and proficiency with buprenorphine, this article answers 10 common questions about laboratory monitoring of patients receiving this medication.

1. Why is laboratory monitoring important?

Proper laboratory monitoring discourages illicit substance use, encourages medication adherence, and influences treatment modifications. Patient self-reporting on medication compliance may be inaccurate or unreliable.[10] Patients who relapse or use other illicit substances may also be reluctant to disclose their substance use.[11]

On the other hand, laboratory tests are objective markers of treatment outcome and adherence, and can verify a patient's self-report.[12] When used appropriately, laboratory monitoring can be therapeutic. It holds patients accountable, especially when used in conjunction with contingency management or other behavioral therapies.[13] Laboratory monitoring is the most reliable method of determining if patients are abstaining from opioids and other illicit substances, or if the treatment plan requires revision.

2. Which tests should I order?

When initiating or maintaining a patient on buprenorphine, order a general urine drug screen (UDS), urine opioid screen (availability varies by institution), urine creatinine levels, urine buprenorphine/norbuprenorphine/naloxone/creatinine levels, urine alcohol metabolite levels, and a urine general toxicology test. It is also recommended to obtain a comprehensive metabolic panel (CMP) before starting buprenorphine,[14,15] and to monitor CMP values at least once annually following treatment. Patients with a history of IV drug use or other high-risk factors should also be screened for hepatitis B, hepatitis C, and HIV.[14,15]

A general UDS can determine if opiates, amphetamines, cocaine, marijuana, or other common illicit substances are present to identify additional substance use. The proficiency of a general UDS may vary depending on the panels used at the respective institution. Some clinics use point-of-care UDS as part of their clinical management; these tests are inexpensive and provide immediate results.[16] A basic UDS typically does not detect synthetic opioids due to the specificity of conventional immunoassays. As a result, specific tests for opioids such as oxycodone, hydrocodone, hydromorphone, oxymorphone, fentanyl, and methadone should also be considered, depending on their availability. Though buprenorphine treatment may trigger a positive opiate or other opioid screen,[17] buprenorphine adherence should be confirmed using several urine tests, including creatinine, buprenorphine, norbuprenorphine, and naloxone urine levels.

In addition to screening for illicit substances and buprenorphine adherence, it is important to also screen for alcohol. Alcohol use disorder (AUD) is highly comorbid with OUD,[18] and is associated with worse OUD treatment outcomes.[19] Alcohol use may also affect liver function necessary for buprenorphine metabolism,[8] so urine alcohol metabolites such as ethyl glucuronide and ethyl sulfate, serum transaminases, and gamma-glutamyl transferase should also be obtained.

3. How frequently should patients be tested?

As part of the initial assessment, it is recommended to order CMP, UDS, and urine general toxicology.[14] If indicated, specific laboratory tests such as specific opioid and alcohol metabolites screens can be ordered. After starting buprenorphine, the frequency of monitoring urine laboratory tests—including UDS, general drug toxicology, buprenorphine/norbuprenorphine/naloxone/creatinine, and alcohol and its metabolites—depends on a variety of factors, including a patient's treatment response and stability as well as availability and cost of the tests. Ultimately, the frequency of laboratory monitoring should be determined on a patient-by-patient basis and clinicians should use their judgment.

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Clinical Point

Laboratory monitoring can hold patients accountable and help determine if a treatment plan requires revision

Lab monitoring in opioid use disorder

Box 1

Buprenorphine: The basics

For patients with opioid use disorder, buprenorphine is indicated for opioid detoxification and maintenance. Oral formulations of buprenorphine (including tablets and buccal films) have long durations of action, and when dosed daily can prevent opioid withdrawal for at least 48 hours.[6] The recommended formulation is a combination of buprenorphine and naloxone, because this formulation is associated with a lower risk of misuse and diversion compared to formulations containing only buprenorphine.[7] However, buprenorphine alone can be effective in patients who experience adverse effects from or are unable to tolerate the combination buprenorphine/naloxone formulation.[7] Despite the addition of naloxone, buprenorphine prescriptions may still be misused and diverted, so close monitoring is necessary.

Buprenorphine is metabolized by the cytochrome P450 system (CYP) (primarily CYP3A4) to its active metabolite, norbuprenorphine, both of which are primarily excreted in feces.[8] However, small quantities of buprenorphine and norbuprenorphine are excreted in the urine,[9] which makes urine specimen the best choice to monitor buprenorphine use for therapeutic purposes.

Clinical Point

The frequency of laboratory monitoring should be determined on a patient-by-patient basis

The American Society of Addiction Medicine suggests testing more frequently earlier in the course of treatment (eg, weekly or biweekly), then spacing it out over time (eg, monthly or quarterly) as the patient's recovery progresses.[14,15] To conserve resources and reduce spending, some clinicians and guidelines recommend random monitoring as opposed to monitoring at every follow-up visit (eg, once out of every 3 to 5 visits, on average), which allows for longer intervals between testing while ensuring consistency with medication and abstinence from illicit substances.[15,16] We suggest screening every 2 weeks for the first month, then spacing out to monthly and quarterly as patients demonstrate stability, with random screening as indicated. Monitoring of liver function should be done at least once annually.

4. How should urine buprenorphine and other results be interpreted?

There are several issues to consider when interpreting laboratory results. The clinician needs to know what to expect in the sample, and what approximate levels should be detected. To check treatment adherence, laboratory data should include stable urine buprenorphine and norbuprenorphine levels and negative urine screening for other illicit substances.[14,15] While urine buprenorphine and norbuprenorphine levels have great interindividual variability due to genetic differences in hepatic metabolism, unusually high levels of buprenorphine (≥700 ng/mL) without norbuprenorphine suggests "urine spiking," where patients put buprenorphine directly into their urine sample.[20,21] Abnormally low or undetectable levels raise concern for medication nonadherence or diversion.

Though urine buprenorphine levels do not reliably correlate with dose, because there is typically not much intraindividual variability, patients should have relatively stable levels on each screen once a maintenance dose has been established.[22] Furthermore, the buprenorphine-to-norbuprenorphine ratio (ie, "the metabolic ratio") typically ranges from 1:2 to 1:4 across all individuals,[20,21,23] regardless of dose or metabolic rate. Urine naloxone levels, which typically are included in commercial urine buprenorphine laboratory panels, also may aid in identifying tampered urine specimens when buprenorphine-to-norbuprenorphine ratios are abnormal or inconsistent with an individual's prior ratio. Naloxone is typically (but not always) poorly absorbed and minimally detected in urine specimens.[20] A high level of naloxone coupled with unusually high buprenorphine levels, particularly in the absence of norbuprenorphine in the urine, may indicate urine spiking.[20,21,23]

Urine creatinine is used to establish the reliability of the specimen. When urine creatinine concentration is <20 mg/dL, the concentration of most substances typically falls to subthreshold levels of detection.[24] If a UDS is negative and the urine has a

creatinine concentration <20 mg/dL, the patient should provide a new sample, because the urine was likely too diluted to detect any substances.

The presence of alcohol metabolites can alert the clinician to recent alcohol use and possible AUD, which should be assessed and treated if indicated.

Liver enzymes should be normal or unchanged with short- and long-term buprenorphine use when taken as prescribed.[25,26] However, acute liver injury may occur if patients inject buprenorphine intravenously, especially in those with underlying hepatitis C.[25]

5. What can cause a false negative result on UDS?

Laboratory monitoring may occasionally yield false negative drug screens. For urine buprenorphine levels, false negatives may occur in patients who are "rapid metabolizers," infrequent or as-needed usage of the medication, patient mix-up, or laboratory error.[27] For other substances, a false negative result may occur if the patient used the substance(s) outside the window of detection. The most common causes of false negative results, however, are overly diluted urine samples (eg, due to rapid water ingestion), or the use of an inappropriate test to measure a specific opioid or substance.[27]

Many laboratories use conventional immunoassays with morphine antibodies that react with various opioid substrates to determine the presence of a specific opioid. Some opioids—particularly synthetics such as oxycodone, hydrocodone, hydromorphone, oxymorphone, fentanyl, buprenorphine, and methadone—have poor cross-reactivity with the morphine antibody due to their distinct chemical structures, so standard immunoassays used to detect opioids may result in a false negative result.[28] In such situations, a discussion with a clinical pathologist familiar with the laboratory detection method can help ensure proper testing. Additional tests for specific opioids should be ordered to more specifically target substances prone to false negative results.[27]

6. What can cause a false positive result on UDS?

The cross-reactivity of the morphine substrate may also result in a false positive result.[28] Other over-the-counter (OTC) or prescription medications that have cross-reactivity with the morphine antibody include dextromethorphan, verapamil, quinine, fluoroquinolones, and rifampin, which can normally be found in urine 2 to 3 days after consumption.[17,27] Poppy seeds have long been known to result in positive opiate screens on urine testing, particularly when laboratories use lower cutoff values (eg, 300 ng/mL), so advise patients to avoid consuming poppy seeds.[29]

For other drugs of abuse, false positives are typically caused by cross-reactivity with other prescription or OTC medications. Numerous substances cross-react with amphetamines and produce false positive results on amphetamine immunoassays, including amantadine, bupropion, ephedrine, labetalol, phentermine, pseudoephedrine, ranitidine, selegiline, and trazodone.[27] Sertraline and efavirenz are known to produce false positive results on benzodiazepine UDS, and ibuprofen, naproxen, and efavirenz can produce false positive results for cannabinoids.[27]

7. How do I communicate the results to patients?

Effectively communicating test results to patients is just as important as the results themselves. A trusting, therapeutic alliance between patient and clinician is highly predictive of successful treatment,[30] and how the clinician communicates affects the strength of this collaboration. A principle of addiction treatment is the use of neutral language when discussing laboratory results.[31,32] To avoid unintentional shaming or moral judgment, use words such as "positive" or "negative" rather than stigmatizing terms such as "clean" or "dirty."[33]

Additionally, make it clear that laboratory findings are not used to punish patients, but rather to improve treatment.[34] Reassuring the patient that a positive screen will not result in withdrawal of care encourages a working relationship.[14] All patients who receive buprenorphine treatment should be

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Clinical Point

The cross-reactivity of some drugs of abuse with prescription or OTC medications may cause a false positive or false negative result

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Box 2

How telehealth changed laboratory monitoring practices

While delivering therapy via telehealth has been shown to decrease the stigma that surrounds treatment, reduce no-show rates, increase retention in care, improve treatment access for patients who have difficulty commuting, and allow for continuity of outpatient treatment during the COVID-19 pandemic, there are also challenges.[40,41] Inducing patients on buprenorphine via telehealth, as well as managing complex treatment cases or repeated failed urine drug screen tests, can be especially challenging. However, treatment standards should be followed as much as possible, and laboratory monitoring as clinically indicated should still be used to improve treatment outcomes.

If needed, patients may be directed to community labs for urine screening and should have results sent to their clinicians prior to the telehealth visit. Complex treatment cases (eg, repeat positive opioid screens, or negative urine buprenorphine screens with comorbid psychiatric conditions) should be handled on an individual basis and in-person appointments may be needed. Video assessment is always preferable to telephone. For patients who are unable to use video and have difficulty maintaining negative drug screens, an in-person visit should be requested.

Clinical Point

Explain to patients that laboratory findings are not used to punish them, but to improve treatment

informed that collecting a UDS is the standard of care used to monitor their progress. You might want to compare using UDS in patients with OUD to monitoring HbA1c levels in patients with diabetes as an example to demonstrate how laboratory values inform treatment.[35,36]

Before reporting the results, a helpful strategy to maintain the therapeutic alliance in the face of a positive UDS is to ask the patient what they expect their UDS to show. When the patient has been reassured that treatment will not be withdrawn due to a positive result, they may be more likely to fully disclose substance use. This allows them the opportunity to self-disclose rather than be "called out" by the clinician.[35]

8. What happens when a patient tests positive for drugs of abuse?

If a patient tests positive for opioids or other drugs of abuse, convey this information to them, ideally by asking them what they expect to see on laboratory findings. Patients may have "slip ups" or relapses, or use certain prescription medications for medical reasons with the intention of establishing abstinence. It is essential to convey laboratory findings in a nonjudgmental tone while maintaining a supportive stance with clear boundaries.

Though addiction specialists often advise complete abstinence from all substances, including alcohol, cannabis, and tobacco, the harm-reduction model emphasizes "meeting patients where they are" in terms of continued substance use.[37] If a patient can reduce their substance use or abstain from some substances while continuing others, these accomplishments should be acknowledged.

For patients who continue to test positive for illicit substances (>3 instances) without a clear explanation, schedule an appointment to re-educate them about buprenorphine treatment and reassess the patient's treatment goals. Consider changing the current treatment plan, such as by having more frequent follow-ups, increasing the dose of the buprenorphine for patients whose cravings are not sufficiently suppressed, switching to another medication such as methadone or naltrexone, or referring the patient to a higher level of care, such as intensive outpatient or residential treatment.

9. What should I do if the results indicate abnormal levels of buprenorphine, norbuprenorphine, and naloxone?

When urine buprenorphine, norbuprenorphine, or naloxone levels appear low or the results indicate a likely "spiking," clarify whether the sample tampering is due to poor adherence or diversion. Similar to dealing with a positive result for substances of abuse, ask the patient what they expect to find in their urine, and discuss the results in a nonjudgmental manner. Patients who admit to difficulty following their medication regimen may require additional psychoeducation and motivational interviewing to identify and address barriers. Strategies to

improve adherence include setting an alarm, involving the family, using a pillbox, or simplifying the regimen.[38] A long-acting injectable form of buprenorphine is also available.

If you suspect diversion, refer to your clinic's policy and use other clinical management skills, such as increasing the frequency of visits, random pill counts, and supervised medication administration in the clinic.[39] If diversion occurs repetitively and the patient is not appropriate for or benefiting from buprenorphine treatment, it may make sense to terminate treatment and consider other treatment options (such as methadone or residential treatment).[39]

10. What should I do if a patient disagrees with laboratory findings?

It is common for patients to disagree with laboratory results. Maintaining an attitude of neutrality and allowing the patient to speak and provide explanations is necessary to ensure they feel heard. Explanations patients frequently provide include passive exposure ("I was around someone who was using it") or accidental ingestion, when a patient reports taking a medication they were not aware was a substance of concern. In a calm and nonjudgmental manner, provide education on what leads to a positive drug screen, including the possibility of false positive findings.

Because a screening test has high sensitivity and low specificity, false positives may occur.[17,27] Therefore, when a result is in dispute, the use of a high-specificity confirmatory test is often needed (many laboratories have reflex confirmatory testing). However, in the case of diluted urine (urine creatinine concentrations <20 mg/dL), patients should be told the findings are physiologically implausible, and a new urine sample should be obtained.[24]

Related Resources

- Li X, Moore S, Olson C. Urine drug tests: how to make the most of them. Current Psychiatry. 2019;18(8):10-18,20.
- Moreno JL, Johnson JL, Peckham AM. Sublingual buprenorphine plus buprenorphine XR for opioid use disorder. Current Psychiatry. 2022;21(6):39-42,49. doi:10.12788/cp.0244

Drug Brand Names

Amantadine • Gocovri
Buprenorphine • Subutex, Sublocade
Bupropion • Wellbutrin, Zyban
Efavirenz • Sustiva
Fentanyl • Actiq
Hydrocodone • Hysingla
Hydromorphone • Dilaudid
Methadone • Methadose
Naloxone • Evzio
Naltrexone • Vivitrol
Oxycodone • Oxycontin
Oxymorphone • Opana
Phentermine • Ionamin
Quinine • Qualaquin
Ranitidine • Zantac
Rifampin • Rifadin
Selegiline • Eldepryl
Sertraline • Zoloft
Trazodone • Oleptro
Verapamil • Verelan

Goals of laboratory monitoring

Laboratory monitoring, including UDS and urine buprenorphine levels, is a mainstay of treatment for patients with OUD. The increased use of telehealth has affected how laboratory testing is conducted (***Box 2,***[40,41] ***page 20***). The goal of laboratory testing is to influence treatment and improve patient outcomes. Clinical data such as clinician assessment, patient self-reporting, and collateral information provide essential details for patient management. However, laboratory monitoring is often the most reliable and objective source by which to influence treatment.

An increased understanding of recommended laboratory monitoring practices may improve your comfort with OUD treatment and motivate more clinicians to offer buprenorphine, a life-saving and disease-modifying treatment for OUD. Doing so would increase access to OUD treatment for patients to reduce the individual and public health risks associated with untreated OUD.

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Clinical Point

When a laboratory result is in dispute, a high-specificity confirmatory test is often needed

Bottom Line

Laboratory monitoring, particularly urine drug screens and urine buprenorphine levels, is the most reliable source of information in the treatment of patients with opioid use disorder (OUD). An increased understanding of monitoring practices may improve a clinician's willingness to offer buprenorphine as an option for therapy and their ability to properly treat patients with OUD.

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Clinical Point

An increased understanding of laboratory monitoring practices may motivate more clinicians to offer buprenorphine

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