Medication-assisted treatment (MAT) Overview: Value of Labcorp's drug testing paradigm including value of norbuprenorphine to buprenorphine ratio (N/B)

Opioid use disorder and treatment

Opioid use disorder (OUD) is a sub-classification of the broader condition, substance use disorder (SUD). While SUD includes dependence on addictive substances like alcohol and stimulants (methamphetamine and cocaine), OUD is specific to overuse, abuse and dependence on opioid drugs. The most common contemporary cause of OUD in the United States is overuse of prescription opioids like oxycodone and hydrocodone and use of illicitly produced opioids like heroin and fentanyl. While fentanyl is also available as a prescription drug, the majority of "street fentanyl" in the U.S. is illicitly manufactured fentanyl (IMF).

OUD is a debilitating condition with high rates of mortality and morbidity.[1] Additionally, patients entering OUD treatment programs exhibit a high rate of relapse. OUD is known to disrupt several aspects of a patient's life, including their interactions with family, coworkers and community. OUD treatment is a complex process. Yet, like many other chronic illnesses, recovery from OUD is possible. National Institutes on Drug Abuse (NIDA) recommends a "whole person approach" to OUD treatment.[1] Most successful OUD recovery programs take a multifocal approach to treatment which addresses medical, psychological, social, occupational, family and legal needs of patients to help in their recovery.

In 2022, an estimated 6.1 million people ages 12 or older reported having an opioid use disorder (OUD) in the U.S.[2] OUD diagnoses in the U.S. are trending upwards with more adults being diagnosed with OUD compared to previous decades.

OUD is diagnosed based on criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Key symptoms observed in OUD patients include a persistent desire and craving for opioids, unsuccessful attempts to reduce opioid consumption, and continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.

Current pharmacotherapies for OUD

There are currently three drugs approved by the United States Food and Drug Administration (USFDA) for treatment of OUD. These drugs include: methadone, a full opioid agonist[3]; naltrexone, an opioid receptor antagonist[4]; and buprenorphine, an opioid receptor partial agonist.[5] These drugs are available in various formulations including oral, sublingual, tablet and injectable forms.[4]

Why is compliance to MAT pharmacotherapy combined with counseling crucial for OUD treatment success and continued recovery?

Relapse is a common and an expected occurrence during OUD treatment. OUD has the highest rate of relapse among the various types of SUD.[6] Lack of access or adherence to prescribed medication-assisted treatment can lead to a rapid relapse. Compliant use of medications like buprenorphine, along with counseling, have shown to be effective for long-term OUD treatment.

Buprenorphine: How does it work and is it effective for treating OUD?

Buprenorphine, a semisynthetic opioid, was approved by the FDA in 2002 as OUD maintenance treatment. Buprenorphine exhibits agonist activity at the mu opioid receptor and an antagonist activity at the kappa opioid receptor. Buprenorphine is available as oral, buccal, sublingual and, more recently, subcutaneous formulations. When taken as prescribed, buprenorphine pharmacotherapy has been shown to reduce cravings, reduce the number of relapse episodes, reduce morbidity and mortality due to opioid overdose, and reduce all-cause mortality.

Methadone, an older drug still used widely for OUD treatment, exhibits full agonist activity at the mu opioid receptor. Buprenorphine is equally effective to methadone for OUD treatment and has distinct advantages compared

to methadone for OUD treatment.[5,7] Buprenorphine can be administered as an outpatient prescribed medication. In contrast, methadone is administered at specifically designated opioid treatment programs (OTP) where OUD patients receive single in-person, observed methadone dose each day. This approach makes OUD treatment with methadone challenging. Additionally, risk of tolerance development and opioid-related life-threatening respiratory depression is significant with methadone.

What is the Mainstreaming Addiction Treatment or the MAT-Act?

Buprenorphine has been available for OUD treatment for over two decades. Yet, studies have shown that this highly effective OUD treatment is vastly underutilized.[8] Only about 22% adults in the U.S. with OUD received pharmacotherapy as a part of OUD treatment in 2021.[5-9]

Regulatory, compliance and systematic challenges toward effectively administering buprenorphine-based OUD treatment has stifled the public's access to this effective drug. Until recently, there were strict procedural requirements for healthcare providers to prescribe buprenorphine, which restricted expanded use for OUD treatment. This procedural requirement is known as the X-waiver.

Several patient advocacy groups had been striving for relaxation of the X-waiver. To expand access to buprenorphine in response to the growing opioid epidemic, the U.S. government passed the Omnibus Bill (Section 1262 of the Consolidated Appropriations Act, 2023), also known as the Mainstreaming Addiction Treatment or the MAT Act. Passing of this bill removed the federal requirement for healthcare providers to submit a notice of intent to prescribe buprenorphine for the treatment of OUD. Removal of the X-waiver requirement is expected to significantly expand the use of buprenorphine for OUD treatment.

Labcorp's medication assisted treatment (MAT) urine drug testing

Urine drug testing provides powerful, actionable information to healthcare providers so appropriate care can be optimized. There are several options available for assessment of compliance to OUD pharmacotherapy. Urine drug testing has shown to be more reliable than patient self-reporting for compliance assessment. Labcorp's MAT Urine Drug Testing Program provides testing options that can be individualized based on the patient's past use history, time in recovery and perceived risk for relapse. The MAT drug testing panels are designed to confirm compliance to OUD therapy and detect use of common illicit or prescribed controlled substances. Drug testing is available in a variety of formats: presumptive testing only, presumptive testing with reflexed definitive testing, or definitive testing by drug class.

Common scenarios in which a healthcare provider may order a MAT urine drug test for OUD patients

- Initiation of MAT pharmacotherapy
- Routine maintenance
- Change of treatment approach
- High-risk behaviors or relapse assessment

Benefits of MAT urine drug testing for patients and healthcare providers

With passing of the MAT act, healthcare providers including physicians, physician assistants, and nurse practitioners with a current Drug Enforcement Agency (DEA) registration with authority to prescribe controlled substances can prescribe buprenorphine for OUD treatment.[10]

Urine drug testing offers patients and providers a variety of opportunities on the journey to recovery and maintenance. Drug test results guide assessment of efficacy and ongoing risk, ultimately influencing treatment plans. Drug test results can be both incentivizing and rewarding. Both expected and unexpected results offer opportunities for ongoing conversation and intervention.

Overall, urine drug testing is a tool that provides patients and providers actionable information to guide next steps in the OUD treatment journey.

How do urine drug concentrations of buprenorphine, norbuprenorphine and naloxone indicate compliance to Suboxone®-based OUD pharmacotherapy?

Urine drug testing is a powerful tool for assessment of compliance to prescribed medications. Presence of an expected drug and its expected metabolite suggests compliance. On the other hand, unexpected negative results for the prescribed medication suggests noncompliance. Additionally, detection of drugs and substances that are not expected allows the healthcare provider to identify high-risk behaviors which typically precede an active relapse to addictive or substance abuse behaviors.

Labcorp's buprenorphine MAT drug testing panels include testing for buprenorphine. When indicated, definitive confirmatory testing includes buprenorphine, the expected metabolite norbuprenorphine, and naloxone, a common constituent of many MAT buprenorphine dosage forms (Suboxone®, Zubsolv®). The ratio of norbuprenorphine to buprenorphine (N/B Ratio) is also provided.

Urine concentrations of drugs and their metabolites vary widely. The patient's hydration status, genetic factors, timing of urine sample collection relative to the last dose of the drug, and drug-specific factors like elimination half-life play a role in determining concentration of the drug and metabolites identified in the urine. Other factors like assay performance and detection thresholds are also important. Labcorp's MAT testing panels provide results in a manner that addresses

some of the variability inherent to urine drug testing. Labcorp's quantitative MAT testing results are normalized to the creatinine concentration in that urine sample. This approach addresses the variability in drug concentrations due to hydration status so that concentrations can be directly compared over time in the same patient.

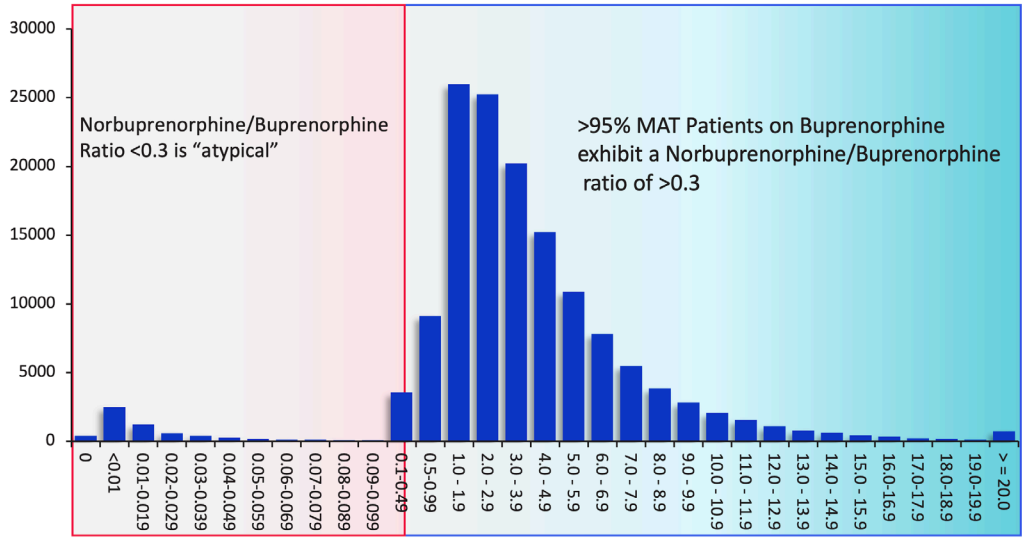
How to interpret norbuprenorphine/buprenorphine (N/B) ratios

N/B ratio provides an additional interpretive dimension to MAT drug testing results. N/B ratio, along with buprenorphine, norbuprenorphine and naloxone concentration, can help identify samples that have been manipulated by "pill-dipping."

Pill-dipping refers to sample manipulation by either physically dipping a pill or by adding small quantities of the drug being tested into the urine sample to simulate compliance. Based on analysis of >100,000 patient results, over 95% of MAT patients on buprenorphine exhibit a N/B ratio >0.3, majority of whose N/B ratio is >1.0. An N/B ratio of <0.3 is an atypical result. An abnormally low N/B ratio may be observed along with a high buprenorphine (typically >700 ng/mL) and a negative norbuprenorphine. If the patient is prescribed a naloxone containing buprenorphine formulation, then naloxone may be elevated (>200 ng/mL). This pattern is indicative of sample manipulation by pill-dipping.[11-13] There are other factors that may cause the pattern, which will be discussed below.

Distribution of Norbuprenorphine/Buprenorphine Ratio

(>100,000 Labcorp patient results 2019 – 2020)



Are there less common factors that can lead to abnormally low N/B ratio? How can healthcare providers address some of these?

- *Drug-drug inhibition*:
  The patient may be co-prescribed known inhibitors of the enzymes that are responsible for buprenorphine metabolism. In these patients, discontinuing the known inhibitors followed by a retest for urine concentrations of buprenorphine, norbuprenorphine and naloxone would help delineate the underlying cause of abnormally low N/B ratio.
- *Timing of collection*:
  The most appropriate window of sample collection for buprenorphine compliance assessment is within 24 hours of the last buprenorphine dose. If the urine sample is collected more than 48 hours past the last dose, there is high likelihood of the sample showing only norbuprenorphine or high norbuprenorphine with low buprenorphine and a resulting abnormal N/B ratio. The key factor that is useful to identify this scenario is the naloxone concentration. In these cases, naloxone concentration is expected to be very low or below the detection threshold. N/B ratio of <0.3 in conjunction with high buprenorphine concentrations (>700 ng/mL) and elevated naloxone concentration (>200 ng/mL) are strong predictors of sample manipulation.

Does Labcorp provide consultative services for interpretation of MAT urine drug testing results?

Interpreting urine drug testing results can be challenging. Accurately interpreting drug testing results has a profound impact on a patient's journey towards recovery from OUD and supports them in reaching their personal health milestones.

At Labcorp, we recognize the unique challenges surrounding clinical drug testing. Information for direct access to our clinical toxicology consultative services is listed below:

- Email inquiries can be directed to **Clinicaldrugtesting@labcorp.com**
- For test menu inquiries, add-on test change requests and result status, call the clinical drug testing support line: **877-474-5767**
- For result interpretation and technical discussion of patient-specific drug testing results, call **866-593-0517**

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