Toolkit for Buprenorphine Practices

AEGIS® Sciences Corporation

Helping Clinicians Make Better Decisions

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Disclosure Statement

The information and resources contained in this document are to educate stakeholders on the purpose and rationale for drug testing in various patient populations and to provide actionable tools to maintain appropriate drug testing practices. This document is for informational purposes and not intended to replace or supersede a clinician's judgment or assessment of the patient.

Other aspects of patient care remain important considerations, such as:

- Review of the state prescription monitoring database (if available), pill counts, patient care agreements, practitioner evaluation and documentation of aberrant behavior, patient counseling and education, possible drug and substance interactions, and any other treatments, interventions, assessments, or patient care activities deemed necessary by the practitioner.
- The ultimate decision of who, when, and how to test a patient for appropriate and inappropriate drug use remains at the sole clinical judgment of the provider.

Background

The opioid overdose crisis is worsening in the United States (US), with nearly 70,000 deaths involving opioids occurring between January and December 2020. Of these deaths, an estimated 83% involved synthetic opioids (excluding methadone), such as fentanyl.[1] In December 2020, the Centers for Disease Control and Prevention (CDC) issued a Health Advisory addressing the dramatic rise in drug overdoses, particularly from synthetic opioids, which coincided with implementation of COVID-19 transmission mitigation strategies. To respond to this epidemic, the CDC recommends expanding treatment access to life-saving and effective medications for opioid use disorder, including buprenorphine, methadone, and naltrexone.[2,3] These three medications are approved for medication assisted treatment (MAT) in combination with behavioral therapy for treatment of opioid use disorder (OUD) and are intended to decrease the physiological cravings and relieve withdrawal symptoms.[4]

Opioid Use Disorder Diagnostic Criteria[5]

In order to confirm a diagnosis of OUD, at least two of the following should be observed within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    - A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    - Markedly diminished effect with continued use of the same amount of an opioid
11. Withdrawal, as manifested by either of the following:
    - Characteristic opioid withdrawal syndrome
    - The same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

Introduction

Many clinicians are joining the fight against the opioid epidemic as a result of legislative changes that have opened the door to expand access to MAT for OUD.[6] Aegis Sciences Corporation recognizes that assessing compliance to a prescribed medication regimen via laboratory testing may not be a familiar process for all practitioners. We hope to provide a summary of regulatory changes and clinical considerations practitioners will need to be familiar with to optimize care.

Founded in 1990, Aegis Sciences Corporation is a laboratory sciences company based in Nashville, TN, which provides science-driven drug monitoring and consulting services for clients such as healthcare providers, pharmaceutical companies, professional and amateur sports organizations, leading college and university athletic programs and Fortune 500 corporations throughout the United States. Many providers involved in the treatment of OUD and substance use disorder (SUD) trust Aegis as a partner in the long-term management of their patients because of the unique testing services designed specifically to meet the needs of OUD/SUD clinicians. Aegis delivers clinically actionable insights related to medication compliance, recent opioid and substance use, and drug-drug interactions to improve patient care, and prevent the human tragedy caused by inappropriate prescription drug or substance use – whether intentional or unintentional – and diversion of prescription medications.

Buprenorphine Availability and Pharmacology[3]

Buprenorphine is a partial mu-opioid agonist that was Food and Drug Administration (FDA) approved for the treatment of OUD in 2002. Buprenorphine has many unique properties at the mu-opioid receptor that characterize its effectiveness for treatment.

Strong binding affinity

- Higher affinity than many full opioid agonists, including fentanyl (6.2 times stronger) and morphine (5.4 times stronger), resulting in blockade of the receptor from other opioids and subsequent effects
- Will displace full opioid agonists from the receptor if given concomitantly in persons who are physically dependent on opioids resulting in precipitated withdrawal

Low intrinsic activity

- Maximum effect of buprenorphine will be less than that produced by agents with high intrinsic activity (e.g., full opioid agonists)
- Results in ceiling effect for respiratory depression, decreased risk of overdose, and reduced potential for misuse
- Increasing doses does not increase the risk of overdose

Slow dissociation

- Results in a prolonged duration of action and long half-life

There are many products FDA-approved for OUD that contain buprenorphine, including sublingual films and tablets and a subcutaneous long-acting injection. Most products are combined with naloxone, a mu-opioid receptor antagonist with minimal sublingual absorption, which was added with the intention of discouraging a person from injecting buprenorphine. Naloxone has been asserted to induce withdrawal if buprenorphine/naloxone is injected in a person physically dependent on opioids.[7,8] However, newer evidence suggests that while naloxone may attenuate the rewarding effects of buprenorphine, this effect will likely be short-lived due to naloxone's very short half-life (30 - 90 minutes). Since buprenorphine has a higher binding affinity to the mu-opioid receptor compared with naloxone, the naloxone may have limited to no effect in patients maintained on buprenorphine. Product selection should be driven by patient preference, naloxone allergy, insurance coverage, and formulary (or cost). The following table includes a complete list of buprenorphine products.

Generic Name	Route of Administration (Frequency)	Brand Names*	Indication(s)
Buprenorphine	Sublingual Tablets (Daily)	Subutex®	Opioid withdrawal and OUD
Buprenorphine/ Naloxone	Sublingual Tablets and Films (Daily)	Suboxone® Zubsolv®	Opioid withdrawal and OUD
Buprenorphine Extended-Release	Injection (Monthly)	Sublocade®	Moderate to severe OUD

*Note: Some brand names may be discontinued; generic equivalents may not be available for all products

Evolution of Buprenorphine Prescribing

Historically, buprenorphine prescribing for OUD was limited to specific providers who satisfied certain certification requirements related to training, counseling, and other ancillary services, and thus received a waiver under the Drug Addiction Treatment Act of 2000 (DATA 2000).[9] Revised legislation in 2021 created a pathway for additional qualifying practitioners to prescribe buprenorphine.[6] Eligible physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives ("qualified practitioners") were exempted from the certification requirements related to training, counseling, and other ancillary services under 21 U.S.C. 823(g)(2)(B)(i)–(ii), allowing them to treat up to 30 patients with OUD using buprenorphine without obtaining special certifications or completing certain training, with opportunity to increase the number of patients receiving treatment over time according to certain criteria and training requirements. Practitioners wishing to prescribe buprenorphine were still required to submit at Notice of Intent (NOI) application under this legislation.

On December 29, 2022, Congress signed the Consolidated Appropriations Act of 2023 (also known as the Omnibus bill) which eliminated the DATA-Waiver Program (X-Waiver) and removed federal requirements for practitioners to submit a Notice of Intent/Waiver to prescribe buprenorphine for the treatment of OUD. Effective January 12, 2023, Substance Abuse and Mental Health Services Administration (SAMHSA) no longer accepts waiver applications. Now all practitioners who have a current DEA registration that includes Schedule III authority, may now prescribe buprenorphine for OUD in their practice if permitted by applicable state law. The previously used DATA-Waiver registration numbers are no longer needed for any buprenorphine prescription. There are no longer any limits or patient caps on the number of patients a prescriber may treat for OUD with buprenorphine. SAMHSA and DEA are actively working on implementation of a separate provision related to training requirements for DEA registration that becomes effective in June 2023.[10,11]

Compliance Assessment Options and Limitations

Numerous compliance assessment tools are recommended in the HHS Buprenorphine Quick Start Guide, including review of the state prescription drug monitoring program (PDMP), pill/film counts, and drug testing.[12] Each practice has its own unique benefits, and use of all three in concert should be considered during treatment of individuals with OUD/SUD.

The PDMP network is better than ever with more states sharing data, and some states uploading new data nearly in real time. However, this only captures legal prescriptions within the data-sharing states. Medication acquired from the street or from another state that does not share data would not be reflected in the PDMP. Also, some interacting medications and substances would not be recorded in the PDMP if they are not controlled substances. Pill counts are used to randomly assess a patient's progression through their prescription. It has been assumed that patients with appropriate quantities of medication on hand are unlikely to be misusing or diverting their medication. However, case reports have been described in literature where patients have rented medication from street dealers in order to produce an appropriate quantity of medication for a pill count.[13] Considerations with drug testing practices are discussed in the next section.

" The patient treated for OUD/SUD is in a fragile state. They have more than likely associated with or continue to associate with persons abusing controlled substances. The current illicit price for buprenorphine is rising at a dangerous rate, increasing the potential of diverting this drug to the illicit market. If the patient is diverting their prescription and not following the therapeutic plan, then a prescriber needs to know to continue to establish the medical necessity of the prescriptions. Testing these patients to ensure their continued treatment and sobriety and to also show adherence to the therapeutic plan is paramount. This lays the groundwork along with prescriber and patient interaction to document medical necessity."

- Richard A. Tucker, Assistant Special Agent in Charge, Drug Enforcement Administration (Retired)

Drug Testing in OUD/SUD

Drug testing provides an objective assessment of medication adherence and substance use, however, not all drug testing methodologies are equal, and some provide limited and unconfirmed information. Point of care (POC) testing provides inexpensive and rapid results, but the methodology may result in false positive or false negative results.[8,14,15] Many POC tests only offer a limited testing menu that is sometimes restricted to identification of a drug class rather than an individual drug and may not include drug metabolites. There is a chance of some substance use going undetected if a provider is fully reliant on POC testing.

Another area in which POC testing may provide incomplete information is with respect to specimen tampering. Definitive testing methods utilizing chromatography and mass spectrometry can identify the absence of metabolites, which may be observed when patients add drug directly to a specimen in efforts to show compliance. Quantitative definitive testing can provide information about the ratio of parent buprenorphine to metabolite norbuprenorphine to offer further insight about the probability of drug being added directly to a sample rather than being ingested. In-depth discussion of buprenorphine toxicology result interpretation is beyond the scope of this document, however, additional resources are available at aegislabs.com.

Synthetic urine specimens may also pass POC testing, whereas definitive testing can identify abnormalities in specimen validity measures. Many synthetic urine manufacturers have adapted to include elements to meet conventional specimen validity testing parameters. However, Aegis provides an additional layer of scrutiny on all urine specimens submitted for testing by performing a proprietary BioDetect™ analysis, which can identify substituted specimens. Because of the presumptive nature of POC testing and the potential for substance use to be mischaracterized, all unexpected presumptive-based tests are recommended to undergo definitive testing.[16-19]

Practitioners should consider each patient's risk for diverting medication, as there is a market for buprenorphine products on the street. A 2014 article in the *Journal of Addictive Diseases* describes interviews with 14 opioid street level pill sellers and the diversion of Suboxone® to recreational drug users.[20] The drug slowly dissociates from opioid receptors which can offer an extended high for non-opioid-dependent users. It can also help mitigate withdrawal symptoms for those that misuse opioids. The ASAM 2020 Guideline Update notes that higher doses of prescribed buprenorphine may increase risk of diversion, so prescribed dose may factor into patient risk stratification and drug testing frequency decisions.[7] Patients who are diverting medication may attempt to add drug directly to their specimen as described above, and definitive testing may be better suited to identify these attempts, since the ratio of parent buprenorphine to the metabolite norbuprenorphine can be quantitatively evaluated.

Although methadone prescribing is not included in the legislative changes surrounding buprenorphine, there are important considerations for opioid treatment programs (OTPs) utilizing methadone. Patients treated with methadone may also benefit from medication compliance testing, even in situations of observed dosing.

Whether patients qualify for in-clinic or take-home dosing, drug testing can show:

- Compliance with prescribed medications, including other medications that may be a part of treatment such as behavioral health medications
- Non-prescribed and/or illicit drug/substance use
- Possible drug diversion

In any clinical setting, definitive drug testing should be considered[21]:

- When presumptive results are disputed by the patient or are inconsistent with patient-reported drug use
- When testing is needed for substances not adequately identified by presumptive testing
- When presumptive results do not align with the clinical presentation of the patient (e.g. negative presumptive results and patient is displaying signs of intoxication)
- When results will inform a decision with major clinical or non-clinical implications

Selecting a Trusted Laboratory Partner

It is important to consider that not all definitive testing is created equal. Clinicians treating OUD and SUD may benefit from a lab that offers a robust test menu in the area of novel psychoactive substances (NPS), including designer opioids and designer benzodiazepines as these drugs carry serious risks, but may not be detected by laboratories with limited test offerings. Synthetic cannabinoids, synthetic stimulants, hallucinogens, dissociatives, and other drugs such as tianeptine, xylazine, and phenibut, may also be drugs of choice for patients with substance use disorder. Identifying use of NPS can reveal dangerous combinations of substances that can have lethal adverse effects, and it can also help characterize a patient's willingness to take uncalculated risks. Simply put, the identification of these substances in patient specimens can save lives.

Advanced specimen validity assessments such as Aegis' BioDetect™ testing may also provide more assurance, as higher risk patients may be more likely to attempt specimen substitution. Approximately 1 in every 200 urine specimens submitted to Aegis reports with unexpected BioDetect™ results which helps clinicians identify high risk patients and get them back on track with their treatment goals.

The ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine document describes criteria for selecting a laboratory, which can be summarized as follows.[21] An appropriate laboratory has:

Experience
working with addiction treatment providers

Flexibilty
in offering testing options that can be individualized to a patient's needs

Available Clinical Staff
for discussion of test results

Information
regarding testing menu, detecting sample tampering, result interpretation, and regional drug use trends

Certifications, Licenses, and Accreditations
appropriate for the testing services provided

An additional service that may vary in availability and breadth from one laboratory to another is drug interaction testing. This type of testing may provide valuable clinical details in patients who show intolerance to prescribed therapy, a reduced response to therapy, or require dose escalations for effective treatment. Patients may also be at increased risk for drug interactions if their medication profile may be incomplete due to the complexity of their past medical history. Also, some patients may be at increased risk of morbidity from drug-drug interactions. Buprenorphine is metabolized by CYP3A4. This enzyme may be induced or inhibited by different drug-drug interactions, which may also impact the ratio of buprenorphine to norbuprenorphine in urine.[22] Methadone can cause a life-threatening arrhythmia known as torsades de pointes, and the risk of this can be exacerbated by drug interactions. Drug interaction testing through a definitive testing laboratory may help minimize the risk of torsades de pointes among patients treated with methadone. Other drug interactions with methadone are possible that may reduce efficacy, increase toxicity, or precipitate withdrawal symptoms.[23]

The Building Blocks of Compliance Assessment for OUD/SUD Patients

Clinical considerations may be generally summarized by the "who, what, when, where, why, and how" of compliance assessment. Practitioners should use their clinical judgment in deciding how to monitor their patients and construct their monitoring protocol. These questions are helpful starting points:

Who will provide and receive treatment as a result of the legislative changes around buprenorphine prescribing?

- How many clinicians within the practice will prescribe buprenorphine for OUD/SUD?
- How many patients will be treated by each clinician?
- What activities will be necessary for new vs. existing patients, and how will these activities fit into the protocol?

What Tools Will Be Used To Build A Medication Monitoring Protocol?

- Patient assessment activities[12]
  - Patient history, including medical, psychiatric, and substance use history
  - Evaluation of family and psychosocial supports
  - PDMP evaluation
  - Physical examination
  - Baseline drug testing[21]
  - Clinical laboratory testing as appropriate (liver function, serum creatinine, hepatitis B and C, and HIV testing)
- Risk evaluation & mitigation
  - Informed consent & treatment agreements
  - Patient education
  - Appropriate visit frequency
  - Strategies to minimize medication diversion risk
  - Referral for higher levels of care as needed
- Monitoring activities
  - Pill/film counts
  - Review of PDMP
  - Drug testing
- Payer evaluation
  - How many services per time period are allowed by the major payers in the practice?
  - What level of service is allowed?

When Will Monitoring Activities Such As Drug Testing Be Performed?

- Drug testing and other monitoring activities are performed at the clinical discretion of the practitioner with decisions generally based on patient risk.
- The results of monitoring activities such as drug testing, medication counts, and PDMP reviews become part of the patient's medical record.
- Drug interaction testing may be necessary depending on the number of medications a patient is taking and their risk of morbidity from drug interactions. As patients stabilize on multiple medications or continue to show risk of polysubstance use with alcohol or non-prescribed drugs, drug-drug interaction testing can highlight additional clinical problems that need to be addressed.

Where Will Care Be Provided – In Office, Via Telehealth, Or Both?

- Can the medication monitoring protocol pivot to serve both settings?
- Aegis offers remote oral fluid specimen collection support so that medication compliance monitoring can continue seamlessly, even in a telehealth setting.

Why Is Each Part Of Treatment Being Performed, And Is Documentation Available To Support Clinical Decisions?

- It is incumbent upon each medical provider to maintain documentation supporting all clinical and treatment decisions. In the event of regulatory, legal, or payer evaluations, such documentation should be readily available. State medical boards, the DEA, and payers may have more specific requirements, but in general:
  - Why was a clinical course of action selected?
  - What happened as a result of the clinical decision?
  - If the outcome was unexpected, what additional decisions were made?

How Will Patient Psychosocial And Behavioral Healthcare Needs Be Addressed?

- ASAM guidelines recommend prompt assessment and referral, if needed, for psychosocial needs and treatment, but initiating buprenorphine treatment is not dependent upon a patient's acceptance or availability of this treatment.
- Treatment success may be enhanced by monitoring compliance with other medications such as those used for depression, anxiety, and psychiatric conditions. A trusted laboratory with a robust testing menu can assist with this type of monitoring.

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