Toxicology in Addiction Medicine

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KEYWORDS

• Pain • Addiction • Management • Drug • Testing • Toxicology

KEY POINTS

- Toxicology testing in addiction medicine varies across the spectrum yet remains a powerful tool in monitoring addictive patients.
- There are many reference laboratories offering toxicology testing, and physicians should have some understanding of laboratory, methodology, testing portfolio, and customer support structure to aid them in selecting the best toxicology laboratory for their patients.
- The definitive drug testing by gas chromatography coupled with mass spectrometry and high-performance liquid chromatography coupled with tandem mass spectrometry are highly accurate if the tests are performed in a good laboratory with technical and toxicology expertise.
- Patients with substance disorders may need to be tested for a wider spectrum of drugs, with greater frequency, over a longer period of time to discourage and identify relapse. In certain instances utilizing oral fluid testing can minimize specimen adulteration-substitution concerns.
- Consultation with a clinical pathologist/toxicologist in conjunction with the consideration of monitoring large numbers of illicit and psychoactive drugs in the addictive patient may provide important clinical information for their treatment.

INTRODUCTION

Toxicology testing is an important standard of care in monitoring the addictive patient. Toxicology tests offer reproducible, unbiased, and objective evidence of chronically relapsing disorder for clinical observation. Drug tests do not provide diagnostic information to identify substance use disorders or physical dependence.[1–3] It is a common observation that drug users minimize or deny drug use. In some instances, drug users provide a partial list of the drugs that they are abusing and hide the other drug use to

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cause a "smoke-screen effect."[1] Drug tests also can improve the communication between the health care provider and the patient. Although a positive drug test result often means that patient had taken a drug, a negative test result does not always mean that the patient did not abuse any drugs. Drug testing is also an important tool in monitoring patients for adherence to their prescribed medications. Urine and oral fluid drug concentration has some limited value but it does not often correlate to the blood concentration.[4] Blood is the only biological matrix that provides therapeutic and toxic concentrations of drugs. The overdose mortality and prescription drug addiction rates in the United States have been increasing due to diverted prescribed opiates, opioids, and benzodiazepines, and we are in the midst of a National Prescription Drug overdose and prescription drug addiction epidemic.[5–8] Often health care providers do not completely trust the drug test results due to the assumption that a drug test gives false-positive and false-negative results. Although there are certain cases in which interfering variables can affect laboratory toxicology results,[9] the clinical toxicology laboratory is capable of providing accurate results for the presence of drugs that are tested, using specific and/or conformational methodologies at the specified cutoff. It is important to note that all clinical laboratories are not the same and there are no set standards on the testing protocols used in clinical drug testing. Furthermore, more than 200 clinical toxicology laboratories appeared in the past 5 years as a result of the lucrative reimbursement system.[10] Thus, as in any profession, it is important to develop an understanding and trust with the laboratory with which a physician chooses to partner toward providing these ancillary services for patient care. In general, clinically relevant reasons for a negative result include the following:

1. The patient has not used that drug.
2. The test did not include that drug.
3. Drug concentration in the biological fluid (urine, oral fluid, or blood) is below the laboratory-established cutoffs.

There are also opportunities for adulteration of a sample, which can also yield a negative result (eg, dilution, oxidants); however, various modalities can be incorporated into a clinical setting to mitigate such possibilities (eg, specimen validity testing,[11] monitored collections). There are multiple technologies available for drug testing. Some of them are simple spot tests that can be performed in the physician's office and they are called Clinical Laboratory Improvement Amendments (CLIA) Waved Point of Care Testing (POCT), an allocation afforded to low-complexity tests. Some of the drug tests are performed on highly sophisticated analytical technique, such as gas chromatography coupled with mass spectrometry (GC-MS) or high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), which are considered high complexity and are therefore not usually available in a physician's office. Each one of these technologies is useful in clinical testing and the physician needs to understand the limitations of these tests. The POCT and the instrumental drug tests are immunoassays; the tests are limited to fewer drugs and these tests also produce false-positive and false-negative results.[12–14] On the other hand, the GC-MS and LC-MS/MS are confirmatory tests and provide definitive presence of the drug and their metabolites at low concentration cutoffs. In addition, there are various kinds of toxicology testing, such as workplace, forensic, performance enhancement, and criminal justice testing.[1,14]

Due to the complexities of various drug tests and technologies, many experts have concluded that most physicians do not have the proficiency in ordering and interpretation of these tests.[1,2,15] The technology in toxicology testing has changed over the past few years and some of the highly difficult analysis of drugs and chemicals that

were previously allocated for pharmaceutical industry use have been applied for use in clinical laboratories with the additional benefit of cost containment to assess multiple drugs and metabolites in one analysis. As a result, the Centers for Medicare and Medicaid Services (CMS) has revised the toxicology testing fee schedule in 2016 and simplified the toxicology testing codes.[16] Although maturation of the technology has afforded a less costly alternative to order large number of drug panels, private health insurance companies are still trying to understand toxicology testing and their applications to the clinical setting in certain respects.

SUBSTANCES OF ABUSE

Legal Versus Illicit

Potentially, more than 130 psychoactive compounds are readily available in the United States, and this includes conventional illicit drugs like cannabinoids, cocaine, methamphetamines, ecstasy, phencyclidine, and heroin, as well as psychoactive prescription drugs like opiates, opioids, benzodiazepines, sedatives, stimulants, and muscular relaxants.[1,2,5] Over the past few years, designer drugs, including stimulants such as bath salts, and synthetic cannabinoid compounds such as K2 spice, have emerged. There are more than 15 synthetic stimulants and more than 35 synthetic cannabinoids on the illegal drug market. These compounds came into the market to mask detection of conventional prescription drug abuse through toxicology testing. It has been observed that as the drug test becomes available for the detection of these compounds, the compounds disappear and new drugs appear,[1] which has provided a new concern for addictionologists as well.

Inpatient Versus Outpatient

It may not be cost justifiable to perform testing on all drugs every time one engages a patient, and the physician may evaluate the necessity for testing rather than provide a blanket test order. Inpatients in a treatment facility may require frequent tests and may include a larger panel, and in the outpatient setting there may not be a need to test the extensive list. However, testing for commonly abused illicit drugs and prescription opiates, opioids, and benzodiazepines are cost-effective based on the 2016 CMS fee schedule, where pricing is based on a tier pricing system (group of drug classes) and not a stacking pricing system that was used until January 2016 for each drug. The true effective drug test is a random drug test, because patients can often abstain from drugs if a predictable time is set for specimen collection.

The addictive patient may change from one drug to another drug if the patient wants to conceal the drug use during a scheduled collection. Therefore, a random test for illicit drugs, opiates, opioids, stimulants, and benzodiazepine may be a reasonable approach. Outpatient testing has more risk, because the patient has a significantly greater chance to relapse as well as access substances of abuse.[1]

Medical Necessity

Any health care test or procedure is required by law to be medically necessary to treat the patient. CMS has published extensive instructions on medical necessity and it is beyond the scope of this article to include detailed regulations on medical necessity. However, a few reminders of medical necessity are as follows: (1) document the test order in the patient medical records; (2) avoid blanket test orders; (3) match the test order with appropriate International Classification of Diseases, 10th Revision coding; (4) review test results and make a clinical decision regarding patient management and document the finding and the decision in the patient medical records. Finally, the physician

needs to use risk stratification.[5,13] For example, if the patient is older and a known alcoholic, then breathalyzer testing with intermittent alcohol and/or ethel glucuronide/ethel sulfate (EtG/EtS) may be appropriate and more cost-effective.[1] Alternatively, if the patient is younger and tests positive for heroin, cannabis, and alprazolam, and is prescribed buprenorphine medication with a concurrent mood disorder prescribed quetiapine after phenobarbital detoxification, then the risk of ingesting synthetic cannabis, and relapse to misusing other benzodiazepines remains a real concern. That patient will require definitive confirmatory (GC/MS or LC/MS) testing for benzodiazepines, because screening (immunoassay) testing may not detect clonazepam, lorazepam, and alprazolam, depending on the antibody construct used in the screening testing method. In addition, the patient will require periodic definitive confirmatory testing for synthetic cannabinoids, although the frequency of such testing is not clear.[1,16]

Forensic Drug Testing Versus Clinical Drug Testing

Different toxicology tests are used in various settings. Workplace drug testing started in the 1980s, and the federal government mandated the testing for federal employees, instituted safety (drug) testing for transportation workers in 1990, and specific drug-testing standards from specimen collection to reporting have been implemented. The program is designed to withstand legal challenges and the system is set to eliminate false positives. A strict chain of custody documentation is followed from collection of the specimen to disposal of the specimen. Extensive guidelines on specimen collection, transport, chain of custody, testing, and reporting have been published in the Federal Register (49 CFR Part 40). Federally mandated workplace drug testing is only for 6 drug classes: cannabinoids, cocaine, amphetamines (amphetamine, methamphetamine), phencyclidine, ecstasy (MDMA, MDA, MDEA), and opiates (heroin, codeine, and morphine only). The testing protocol is a screen by laboratory-based immunoassay (EIA) at the specified cutoff and confirmation of any presumptive positives (via EIA) using definitive tests like GC-MS or LC-MS/MS. All results are reported to a medical review officer (MRO) to make the final decision on a positive result. The MRO may turn a positive result to negative if there is a legitimate prescription for the positive drug. All these protocols are to legally defend the positive drug test in an administrative or court hearing.[1]

Clinical drug testing is part of a patient's examination performed by a clinician with whom the patient is in a therapeutic relationship. The clinical toxicology test is used to identify the presence of drugs and chemicals in the patient, which provides ancillary objective information to aid the clinician in partnership with the patient in appropriate patient management. The clinical drug test must eliminate false-positive and false-negative results. The drug detection window is inversely proportional to the cutoff concentration: the lower the cutoff the longer the detection window. The cutoff concentration should be as low as the technology can provide, in concert with the clinical application value; extremely low cutoff values run the risk of false positives, which occur as a result of methodological interferences[17,18] rather than presence of the actual drug, and must be accounted for when cutoff values differ from laboratory to laboratory. Addiction patients should be tested at zero-tolerance level, which is the limit of detection for the test. The clinical drug test often includes many more drugs than workplace drug testing. Therefore, the workplace drug testing model is not always appropriate for the clinical setting.[1,10]

Medically Assisted Treatment

Medication-assisted treatment (MAT) often refers to addiction intervention with pharmacopeia, such as methadone or buprenorphine. In both cases, the toxicology test is

used to ensure that the patient is (1) taking the prescribed drugs, (2) not taking another nonprescribed opiate or schedule II-V medication, and (3) not taking an illicit substance or alcohol. Unlike pain management, or other disciplines, a positive test in addiction medicine is handled much differently.

A positive test for a nonprescribed schedule II-V medication or illicit substance is addressed with intervention rather than discharge, just as would absence of the MAT opiate (buprenorphine or methadone). However, without getting into details, due to federal regulations, it may take at least one week before a methadone patient can be titrated up to their maintenance dose. Therefore, it is not uncommon for them to be "chipping" away at heroin until they can receive the full amount of MAT needed to cut the heroin craving. Thus, their urine will still test positive for opioid under "OPI" or "MOP" (depending on the presumptive cup or dipstick POCT that is used) and 6-acetylmorphine, the metabolite specific for heroin which should be sent to the laboratory for LC-MS/MS or GC-MS for definitive confirmation.

Toxicology testing serves to determine if MAT is effective, or requires a higher dose or application of the American Society of Addiction Medicine Criteria,[5] to increase the level of care to the next appropriately elevated treatment level. Rarely is a toxicology test result used to discharge a patient in addiction medicine, but rather warnings, and adjustments to the treatment plan are implemented. In the outpatient setting, toxicology testing is more dependent on the type of environment. For example, an Opioid Treatment Program (OTP) usually has the staffing to administer and monitor drug testing, whereas an office-based buprenorphine provider managed by a solo practitioner may have limited to no staff. In addition, methadone OTP uses the toxicology results as a reward, as compliance allows the patient "take home" privileges, whereas the office-based buprenorphine provider often starts off at 30 days, based on the level of training, which varies. Of interest is that there still remains a significant number of other illicit drugs, similar to pain management patients, at any time in the MAT outpatient setting, that may be detected by toxicology testing. A review found at least 30% of patients in methadone recovery tested positive for cocaine on average,[19] thus further highlighting the importance of toxicology testing in such risk-oriented settings. Finally, the known history of co-occurring disorders in substance abuse, including anxiety, depression, attention-deficit/hyperactivity disorder, bipolar disorder, and others, leads to higher incidence of patients being treated by physicians who do not know about the patients' methadone ingestion and/or may not yet participate in their state specific Prescription Drug Monitoring Program (PDMP). Thus, toxicology testing can help assess other medications that (1) the patient fails to disclose (PDMP can have a 2–3-week delay) and (2) is newly published as abuse potential, like gabapentin.[20]

SUBSTANCES

Although there are multiple substances that are available as a source for potential addiction, either as subsequent abuse in the course of pain management or via recreational means, the following represents common agents that are normally associated with addiction as well as those related to MAT to manage their use.

Alcohol

Blood is the ideal specimen for monitoring recent use of alcohol, and the detection window of alcohol in blood is only few hours.[21] Urine alcohol also has a short window, and diabetic patients may produce alcohol by fermenting the sugar in the urine. EtG and EtS are metabolites of alcohol and the detection window can be longer commensurate with alcohol ingestion: $\leq$24 hours after intake of $\leq$0.25 g/kg ethanol, and for

≤48 hours after intake of ≤0.50 g/kg ethanol. Patients who are alcohol dependent can increase the detection times for urinary EtG and EtS from 75 to more than 90 hours during recovery from heavy drinking, thereby dubbing EtG/EtS the "80-hour" alcohol markers.[22] Care must be taken to interpret the EtG and EtS results because exposure to alcohol from various sources (wipes, mouthwash, alcohol-containing cold remedies, and some fermented drinks) could cause positive ethanol, EtG, and EtS.[23,24]

Heroin

Heroin metabolizes immediately to 6-monoacetyl morphine (6-MAM) and morphine. In a very small percentage of patients, only 6-MAM was detected, and the morphine concentration was very low or undetectable. Therefore, the 6-MAM test is important in the addiction treatment setting. A small amount of codeine may present in most of the heroin preparations, and the typical ratio of morphine to codeine is 2:1 or less. In addition, there is a concomitant increase in heroin deaths, with evidence of a mixed-in component of nonprescription (illicit manufactured) fentanyl.[14,25] Ascertaining whether mortality occurred due to prescription fentanyl versus illicitly produced fentanyl cannot be deduced through forensic toxicology, although prescription records can clarify whether the deceased had a valid prescription, along with cause-of-death police reports.

Although prescription opioid mortality still exceeds heroin mortality nationally by almost 4:1, Ohio, having been 1 of the first 2 states after Florida, to implement such legislation in 2012 (House Bill 93), has seen an interesting statistical outcome. The Centers for Disease Control and Prevention's Morbidity and Mortality Report for 2013 actually had heroin deaths significantly exceeding prescription opioid deaths, but then in 2014 they approximated each other, only because fentanyl was classified under the rubric of prescription opiate (synthetics) even if "illicit."[26] Such changes in classification can affect trend bias and reporting since another detailed study showed that a crime scene sample could delineate illicit versus pharmaceutical fentanyl in certain cases.[25]

Methadone

Methadone metabolizes to normethadol and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and both methadone and EDDP metabolize to glucuronide conjugate. Methadone without EDDP is most likely due to pill scraping. Most of the POCT is formulated for methadone, and there is an immunoassay reagent available for the metabolite EDDP. Therefore, EDDP may be a better test in monitoring methadone patients. At any time across the United States, there is an approximately 30% incidence of cocaine use in patients at methadone clinics. Also, currently, methadone clinics do NOT report on the state PDMPs, so more often than not, patients with comorbid addiction/pain who cease with their methadone treatment will end up back in a pain practice transition to oxycodone with the explanation that the oxycodone was obtained from a friend or relative (~55% of nonprescribed opioids/opiates). This also supports the need for a very broad-based definitive toxicology testing approach on the initial intake for recovery patients.

Buprenorphine

Buprenorphine metabolizes to norbuprenorphine, and both buprenorphine and norbuprenorphine form a glucuronide conjugate. Immunoassays, both POCT and laboratory-based tests, do not cross-react with glucuronide metabolites and could give false-negative results. Definitive testing by LC-MS/MS may be ordered on these false-negative specimens. Pill scraping (or putting a fraction of the "Suboxone" strip

into the urine) is commonly used by these patients to falsely demonstrate that they are taking their medication as prescribed. However, in such cases, the presence of buprenorphine without the metabolite norbuprenorphine can indicate that the patient added a small portion of the pill into their urine.

Overall, toxicology testing in addiction medicine varies across the spectrum, yet remains a powerful tool in monitoring addictive patients. There are various types of drug-testing devices available for a physician's in-house office testing requirements and most of these are useful testing devices. However, these devices have limitations, and the physicians should understand their limitations. Also, there are many reference laboratories offering toxicology testing and physicians should have some understanding of laboratory, methodology, testing portfolio, and customer support structure to aid them in selecting the best toxicology laboratory for their patients. The definitive drug testing by GC-MS and LC-MS/MS is highly accurate if the tests are performed in a good laboratory with technical and toxicology expertise. Moving from urine to oral fluid testing reduces the privacy concerns and minimizes the specimen adulteration-substitution issue. Patients with substance disorders need to be tested for a wider spectrum of drugs over a longer period of time to discourage and identify relapse. Drug testing should be similar to general clinical diagnostic testing in which patients are monitored for diseases like diabetes and hypertension.[27,28] Furthermore, the new CMS fee schedule made it possible to monitor a large number of drugs at a reasonable cost. To this end, consultation with a clinical pathologist/toxicologist[29] in conjunction with the consideration of monitoring large numbers of illicit and psychoactive drugs in the addictive patient may provide important clinical information for their treatment.

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