

Toxicology in Pain Management



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KEYWORDS

• Pain management • Pain medicine • Toxicology • Drug testing

KEY POINTS

- Urine toxicology testing can prove very useful for drug assessment, prescribing and monitoring approaches in pain management.
- Drug testing provides an objective measure of assessing risk stratification in conjunction with the patient's medical, psychiatric and compliance history.
- Understanding drug metabolism, biological fluid matrices as well as the differences and limitations of presumptive (screen) versus definitive (confirmatory) testing methods are critical to effective and appropriate patient management.

INTRODUCTION

Toxicology monitoring has become the standard of care in providing objective laboratory data toward managing chronic pain patients, whether cancer or chronic non-cancer pain (CNCP). Recent guidelines issued by the Centers for Disease Control and Prevention (CDC) for prescribing opioids for chronic pain recommend urine drug testing before starting opioid therapy and periodically monitoring for prescribed medications as well as controlled prescription drugs and illicit drugs. The literature is extensive regarding the frequency and general methods of testing in the pain medicine journals,¹⁻³ by the American Pain Society (APS) and the American Academy of Pain Medicine⁴ (AAPM), plus the more recently formed subspecialty board for interventional pain, established under the American Society of Interventional Pain Physicians⁵ (ASIPP). The main difference among these societies is regarding the definition of chronic pain; APS and AAPM define chronic pain as persisting beyond the normal tissue healing time of 3 months,⁴ whereas ASIPP originally defined it as 6 months^{6,7} and then adjusted it to 3 months.⁸ Regardless, the goal of this review is to present an

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overview on the indications for toxicology testing primarily in CNCP, including frequency based on risk stratification, select medications, or drugs and their metabolism, regulatory and legal oversight that impact testing approaches, differences, and limitations in screening versus confirmatory testing methodologies, as well as sample matrices, and some algorithms the clinician may apply to insure medical necessity and evidence-based standard of care.

General Approaches to Toxicology Monitoring in Pain Medicine

Drug testing is vastly misunderstood and underutilized in health care. In addition, the term “urine drug testing” has generically been used for all types of drug testing. Urine drug testing is somewhat of a catch-all term because there are various types of urine drug testing the physician can use to monitor pain management patients.^{9,10} Urine drug testing is used to monitor compliance with prescription medication and to identify substances prescribed as well as those that are not expected to be present. There are hundreds of chemicals, both licit and illicit, used today, especially with the emergence of synthetic psychoactive drugs; thus, it is impossible to test each drug in every patient. The most prevalent abused classes of drugs are marijuana, opiates, opioids, cocaine, benzodiazepines, and other sedatives.

Drug testing is performed in diverse settings, such as employment, criminal justice, clinical diagnosis, and monitoring of addiction patients in treatment. Each of these settings is intended for distinct purposes. For example, the Department of Transportation and the Federal Employee Drug Testing systems use the Mandatory Guideline (CFR 49, Part 40), the gold standard in the employment setting.¹¹ It is a deterrent program and safeguards against potential false positives. The Federal Workplace Program mandates administrative cutoffs and any drug at or above that set cutoff is reported positive, and any drug below the established cutoff is reported negative. However, a negative result does not mean the patient has no drug in their system; it simply says the drug level is below the cutoff. It is important to note that a laboratory cutoff is established by standard controls that determine the range of concentration that is allowed to be reported to the clinician; these operational aspects are tightly regulated by governmental and accrediting bodies, and nonadherence to such can result in fines, penalties, and laboratory suspension or closure. Therefore, the Federal workplace protocol can be misleading in the clinical setting, where a negative result could be positive in the realm of a lower limit of detection cutoff. Furthermore, the pain management drug test must eliminate false positive and false negative results for patient care.

The Federal Program only tests for 6 classes of drugs: amphetamines, marijuana metabolite, cocaine metabolite, opiates (codeine, morphine (M), and heroin metabolites only), ecstasy, and phencyclidine. However, pain management testing is a clinical test which includes illicit drugs, opiates, opioids, benzodiazepines, sedatives, and muscle skeletal relaxants. Thus, clinical drug testing is mainly used in pain management, addiction treatment, and psychiatry. Physicians may prescribe opiates and/or opioids in a wide range of doses to treat a patient’s pain. These prescribed drugs can also interact with illicit drugs, other psychoactive drugs, sedatives, and alcohol, which could be lethal in patients on chronic pain medications, where higher doses of opiates or opioids are often prescribed as tolerance builds. As a result, the physician needs to monitor these patients periodically for the presence of the prescribed medication as well as other nonprescribed opioid and/or sedatives in the patient’s system. The detection time is longer when the drug cutoffs are lower in accordance with absorption, distribution, metabolism, and excretion and steady-state kinetics. For example, cocaine can be detected up to 5 days at a 25-ng/mL cutoff versus 2 days at a 300-ng/mL cutoff. Further, illicit drugs, benzodiazepines, and/or alcohol,

along with psychoactive drugs, can put health and safety at risk due to drug interaction. To this end, although toxicology testing can provide objective assessment of drug profiles to aid the physician in narcotic/analgesic prescribing options, understanding the testing cutoffs and the differences in reporting that they may avail will provide greater utility to patient management.

There is an “opioid epidemic” described as overprescribing, with a decade-long national trend of increased prescription opiate deaths, often in concert with other narcotics/analgesics/anxiolytics (ie, benzodiazepines). Currently, some states, Florida being the first, because of the Oxycontin pill mills, have already passed aggressive legislation, and others are rapidly in the midst of similar bills, limiting amounts of prescription opioids (morphine equivalent dosage [MED]) to board-certified pain specialists, percentage of pain patients per total practice allowed, mandatory Prescription Drug Monitoring Programs (PDMPs) (49 states, Missouri being the exception), and even initial limits on first-time opioid prescriptions to 7 days (with exceptions). Washington was the second state to have similar legislation, specifically “Do not exceed 120 mg of oral morphine equivalents/day without either demonstrated improvements in function and pain or first obtaining a consultation with a pain management expert,” and has had their third revision since June 2015, including functional assessments like the Oswestry Disability Scale.¹²

This field is ever changing. However, the focus should remain on the core evidence-based practice of clinical toxicology as it relates to Pain Medicine rather than the epidemiologic study of opioid abuse.

INDICATIONS FOR MEDICATION MONITORING/DRUG TESTING

The key reasons behind toxicology testing in pain management patients are based on the principles that lead to drug interaction, overdose, and basic patient safety issues. The following list shows the reasons the overall mortality has increased significantly over the past decade from prescription medications:

1. Increase in total opioid prescriptions
 - Americans, who account for 4.6% of earth’s population, consume 80% of the world’s produced prescription opioids and 99% of total hydrocodone, according to the ASIPP fact sheet (www.asipp.org)
2. Methadone
 - 5% of opioid prescriptions = one-third of opioid-related deaths
 - Physician errors in methadone prescribing (eg, initial dosing, dose titration, opioid rotation to methadone).
 - Payers promote methadone as first-line therapy (significantly lower cost vs other opioids)
 - Torsades de pointes
3. Coadministration of other central nervous system depressants (may be with or without prescriber knowledge)
 - Benzodiazepines
 - Alcohol
 - Antidepressants
4. Unanticipated medical or psychiatric comorbidities
 - Depression
 - Substance-use disorders
 - Sleep apnea
5. Patient nonadherence to regimens
 - Escalating doses without prescriber knowledge

Risk Stratification

Before prescribing opioids to any patient, the standard of care requires that the physician undergo risk stratification using basic history with simple screening tools to assess personal and family history of substance use disorder, mental illness, tobacco use disorder, or alcoholism. Failure to do this is below the standard of care in the community and is leading to increased scrutiny by the State Medical Boards, the Drug Enforcement Agency, which can now request patient records in addition to dispensing logs,¹³ as well as civil litigation.¹⁴ The most common and well-validated screening tools for opioid-naïve patients include the Opioid Risk Tool developed by Dr Lynn Webster¹⁵ with the Screener and Opioid Assessment for Patients with Pain, which has been revised to include aberrant behaviors¹⁶ and can then be subsequently cross-validated to included chronic pain patients.¹⁷ Patients with alcohol history initially should be screened with any of the alcohol risk screening tools: CAGE (Cut down, Annoyed by criticism, Guilty, and need Eye-opener next morning), MAST (Michigan Alcoholism Screening Test), and AUDIT (Alcohol Use Disorders Identification Test).¹⁸ However, pain management practices may not routinely perform the alcohol screening tests.

Compliance history

Any patient should have a review of risk factors to help guide the frequency of toxicology testing, and which substances to test for based on prior compliance history. Risk assessment by compliance history should occur whether for an existing patient, or a referred patient, based on the referring physicians records. Obviously, accepting a discharged patient for compliance issues will most likely continue to be a high-risk patient. Having the toxicology records will help direct the type of testing and initial frequency. It will also support the “Medical Necessity,” which is an important component. The physician and the laboratory must justify which tests to order and frequency of such tests. Toxicology testing must be based on risk stratification, regardless of presumptive or definitive testing.

Psychiatric history

Comorbid disorders are a commonly missed cause of opioid misuse and are associated with, or lead to, overdose deaths. A common scenario is that the patient is concurrently seeing a psychiatrist that, despite the standard of medical care, is also being prescribed alprazolam for chronic anxiety rather than acute anxiety. Toxicology testing is done for patient safety, because many patients are not aware of the high risk that opioids and benzodiazepines have in combination. Several co-occurring mental illness disorders are frequently associated with substance misuse or abuse and need to be screened before proceeding with opioids in CNCP patients.^{19,20} Utilization of the brief General Anxiety Disorder 7-item scale and Patient Health Questionnaire 9-item for depression screening, two common aspects in pain management, goes far in helping diagnose and treat common comorbid mental health aspects of chronic pain. They are a critical component of risk stratification to help determine frequency of toxicology testing and risk of compliance.

Medical necessity

An initial baseline drug test should be performed before prescribing opioid medication, and certain medications should be verified using definitive (“confirmed” or “quantitative”) rather than presumptive (“screened” or “qualitative”) testing. Overall, most of the literature quotes around 11% of all pain patients of any sex, demographic, race, or age are using an illicit drug. Nonprescription, or sometimes called, nonmedical opioid use,

occurs between 20% and 40% in an average pain management population, regardless of the same demographics noted. Thus, the initial toxicology test needs to include any and all opioids, opiates, illicit, benzodiazepines, sedatives, cannabis, common synthetics for the demographic and geographic range and should be definitively tested, where appropriate, at the laboratory level.

The Center for Medicare and Medicaid Services indications The following indications are directly from the Center for Medicare and Medicaid Services (CMS) Web site as indications for a presumptive drug test (immunoassay):

In whom illicit drug use, non-compliance or a significant pre-test probability of non-adherence to the prescribed drug regimen is suspected and documented in the medical record; and/or In those who are at high risk for medication abuse due to psychiatric issues, who have engaged in aberrant drug-related behaviors, or who have a history of substance abuse.

In the case of chronic pain, specifically as discussed here, CMS further describes its indications as such:

- Determine the presence of other substances before initiating pharmacologic treatment
- Detect the presence of illicit drugs
- Monitor adherence to the plan of care

These same guidelines are suggestions that follow commercial payers as well, in terms of medical necessity for medical reimbursement. Basically, toxicology testing affords safety of the patient to insure they are not taking medication or psychoactive drugs, which, combined with prescription pain medication, can lead to toxic levels and/or overdose. In addition, such testing insures the patient is being compliant by taking the prescriptions as directed under the guidance of the physician, rather than taking other nonprescribed pain medication, illicit substances, or diverting. Unfortunately, despite the best science, today's toxicology, regardless of the matrix, will not provide an actual steady-state pharmacokinetic value. However, the combination of pill count, random testing and specimen validity will provide the closest metric to curb diversion and help prevent such activity. It is important, in this instance, to highlight that toxicology testing provides objective ancillary data to the clinician to help manage the patient in concert with other components of the medical gestalt, which differs with each patient.

Metabolism of common medications

Understanding the metabolism of the pain medication is integral to knowing what parent drug and metabolites to test for in plasma, oral fluid, and urine. These pathways are briefly reviewed for the most common medications used, and the parent-metabolite relationships that will show in the urine, which currently represent the ideal evidenced-based clinical matrix, although a plethora of literature has been published in the last few years validating oral fluid testing.

Morphine

Morphine (M) is the mainstay drug with which most others are compared, for purposes of many state regulations. It is produced from codeine and heroin metabolism. Primary metabolism is via phase II hepatic pathway by glucuronide (G) conjugation via uridine 5'-diphosphoglucuronosyltransferase (UGT) using several variations of the enzyme to morphine-6-glucuronide, M-6-G (active), morphine-3-glucuronide, M-3-G (inactive), and an array of several metabolites, including morphine 3,6-diglucuronide,

M-3,6-G, normorphine (via N-demethylation), and others. Finally, of interest is that M, through a yet unknown pathway, can metabolize into hydromorphone (HM) as a minor metabolite.

A case example is a Caucasian female patient using opioid rotation to wean down from overprescribed oxycodone 720 mg/24 hours (1080 morphine equivalent dosage [MED]) by 25% reduction for cross-tolerance to M dosed 800 mg/24 hours using opioid rotation. The objective urine definitive report using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) shows HM. This pathway is more common in women on higher doses of M, but usually does not exceed 6% of the M concentration. In the urine, one should find 75% as M-3-G, 10% free M, 4% conjugated normorphine, 1% free normorphine, and trace M-6-G, M-3,6-G, M-3-sulfate plus HM.²¹ However, others quote 55% M-3-G, 10% free M, 15% M-6-G plus 6% HM²²; such variations can also be observed within and between patients and can be due to differences in liver/kidney function, polypharmacy, hydration status, dosing among others.

Codeine

Codeine is a prodrug (the only opioid/opiate formal prodrug), which has no analgesic effect until activated by the liver. The primary activation is phase I: (1) O-demethylation via cytochrome P450 enzyme (CYP2D6) to M and (2) N-demethylation via CYP3A4 with minimal HM from M.²³ Other metabolites, as described later in this review, include hydrocodone, which further metabolizes to dihydrocodiene and norhydrocodone as well as HM. An example wherein a patient on codeine only demonstrates hydrocodone and HM may be due to their being a fast metabolizer as well as the time of ingestion, hydration status, and the like, although diversion and surreptitious ingestion of hydrocodone cannot be excluded. Such a result can be elucidated with focused patient dialogue, scheduled or unscheduled retesting, as well as switching to another medication that should not result in any metabolites being present in the urine.

Hydrocodone

Hydrocodone, an active analgesic, undergoes (1) O-demethylation via CYP2D6 into HM and (2) N-demethylation into minimally active norhydrocodone. A minor pathway for both hydrocodone and HM is 6-keto-reduction as (1) hydrocodone into 6 α and 6 β hydrocol and (2) HM into 6 α and 6 β hydromorphol.²¹ Finally, HM is further metabolized by phase II via UGT into hydromorphone-3-glucuronide (HM-3-G).²⁴

In blood and oral analysis, the primary metabolite is parent hydrocodone followed by norhydrocodone, and significantly less HM.²⁵ The benefit of oral analysis is the consistent presence of norhydrocodone with a hydrocodone:norhydrocodone (HC:norHC) ratio of 1:16, and minimal HM, which helps delineate the patient is taking hydrocodone rather than HM.²⁶ Urine analysis reveals 26% hydrocodone eliminated in 72 hours, with results as follows: (1) hydrocodone, 9% to 12%; (2) norhydrocodone, 5% to 19%; (3) HM-3-G, 2% to 4%; (4) 6 α and β hydrocol, 1% to 3%.²¹ HM is always present in its conjugated form.²⁷

Hydromorphone

Hydromorphone (HM) is primarily metabolized by UGT at the 3 position to HM-3-G, and some 6-keto-reductase into 6 α and 6 β hydromorphol as noted in the prior section. One opioid review mentions HM-6-G,²⁸ which is a minimal amount, verified by the original article,²⁹ in conjugation with any 6-moeity that is not supported due to the presence of a ketone at the 6 position,³⁰ which is the key differentiation between M (hydroxyl at 6) and HM. Blood concentration finds HM-3-G ~ 25 times parent HM, whereas oral fluid is highly variable and inconsistent with significantly lower thresholds

required.²⁶ Most data unfortunately are from hydrocodone studies, because there is a paucity of HM metabolism data in oral fluid. Urine finds at least 35% conjugated at HM-3-G, 6% free HM, and the remainder at H-3-sulfate, H-3-glucoside, the 6-keto forms, while chronic pain patients may find primarily HM-3-G without free HM.²¹ A final note, in renal failure, both M and HM, being conjugated into 3-glucuronide, have been found to build up to potentially neurotoxic levels. One must take caution with M and HM in renally compromised patients of the M-3-G and HM-3-G levels, which lead to neuroexcitatory toxic responses in those individuals.

Matrices

Urine is the preferred biological fluid for drug testing for many years, and it is a matured technology. It is widely used in toxicology testing for years using various analytical techniques. Typically, the concentrations of drugs in urine are multiples higher than other matrices, and the drugs can be detected for 2 to 3 days. It is important to note that urine drug concentration, however, does not correlate to the dose. Unfortunately, urine is easier to adulterate than most other matrices. Hair, oral fluid, and blood are good biological matrices; however, the drug concentrations are low.³¹ As a result, the matrices other than urine testing require highly sensitive LC-MS/MS instrumentation and scientists with more training in the technology.

Oral fluid is becoming a viable matrix for illicit and prescription drugs. Drug concentrations in oral fluid are 50-fold lower than in urine, and a highly sensitive analytical technique with high level of expertise is required to perform drug testing in oral fluid samples. Oral fluid collection is easy and noninvasive, and it is difficult to adulterate. Recent studies show that oral fluid has some correlation to the blood concentration, although not a direct correlation, and it varies with the drug. The notable difference is that cannabis detection time is significantly longer in urine when compared with oral fluid. The reason is because cannabis metabolites are detected in urine, whereas oral fluid detects the active parent compound, Δ -9-tetrahydrocannabinoid. Overall, oral fluid is the least invasive collection and is a viable biological matrix in clinical drug testing. However, oral fluid testing can be affected by ingestion of other items, hygiene, pH, and transport among others.³²

Drug concentrations in blood have therapeutic, toxic, and impairment values; however, blood collection is highly invasive and requires a licensed phlebotomist to collect the blood. Furthermore, urine drug concentration does not correlate directly to the blood-drug concentration.

All these biological matrices have been used in clinical drug testing. Typically, drug detection in urine is 2 to 3 days, and certain drugs can be detected in hair for 30 to 90 days. Oral fluid and blood may have shorter detection windows, and the lower drug cutoff concentrations could match oral fluid detection window close to the urine detection window for opiates, benzodiazepines, sedatives, and stimulants. However, the oral fluid and blood marijuana detection window is only 1 to 2 days compared with 3 to 30 days in urine. Appreciating that there are differences in parent/metabolite relationships when testing different fluid matrices helps in matrix test selection and subsequent result interpretation. For example, urine marijuana test is for the carboxylic acid metabolite of the active compound delta-9-tetrahydrocannabinoid (Δ 9THC-COOH), and oral fluid and blood test is for the active compound delta-9-tetrahydrocannabinoid (Δ 9THC).

Presumptive Versus Definitive

Clinical drug testing typically uses two testing technologies: (1) point-of-care testing (POCT) using strips or cups, or instrument-based immunoassay test (analyzer), and

(2) the laboratory-based chromatography coupled with mass spectrometry tests (GC-MS and LC-MS/MS). The POCT and analyzer give immediate results to the physician for immediate treatment decisions. Both analyzer and POCT are formulated with specific drug antibodies for competitive binding with labeled drugs to the drugs in the urine specimen. The POCT and analyzer are immunoassays and are formulated for a specific drug in a class of drugs such as opiates and benzodiazepines. As a result, some of the drugs in that class have poor cross-reactivity with the assay and give false negative results (Fig. 1). There are various immunoassays that are US Food and Drug Administration (FDA) 510K cleared today, such as Enzyme Multiple Immunoassay, Kinetic Interaction of Microparticle in Solution, and Cloned Enzyme Donor Immunoassay. All immunoassays are identical as a general principle, and there may be some cross-reactivity, with one drug better than another. The immunoassays are formulated with one drug in a class of drugs for 100% cross-reactivity, and the other drugs in that class vary with the antibody the manufacturer has produced. For example, opiate immunoassay is formulated with M, and benzodiazepine immunoassay is formulated with oxazepam. As a result, for the opiate immunoassay where M is the principal drug used in the formulation, in testing for HM, hydrocodone, and oxymorphone, all have very poor cross-reactivity and may give false negative results. Furthermore, one type of immunoassay may have lower cross-reactivity for hydrocodone than the other immunoassays, and none of the immunoassays are formulated or FDA 510K cleared for hydrocodone, oxycodone, HM, or oxymorphone. For this

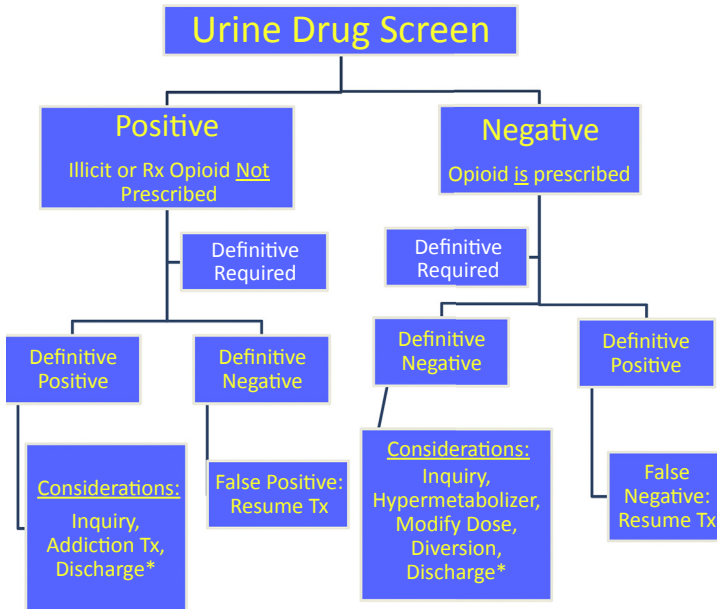


Fig. 1. Sample urine drug testing algorithm for discrepancies. Flow chart represents possible approach when urine drug screen expectations do not correlate with medical prescription documentation. Scenario depicts opioid drugs but can be extrapolated for other drug classes. "Screen" refers to POCT or EIA and "definitive" refers to LC/MS confirmation testing methods as described in the text. Inquiry refers to discussion with patient on drug administration, compliance, dosing, consistency, etc., as described in the text. *Patient discharge depends upon the relationship with the patient, risk assessment and other factors described in the text.

reason, a false negative result for many drugs can occur with immunoassay in certain drug class. Because POCT cups and strips are also immunoassays, similar limitations exist.

Benzodiazepines are another class where immunoassay has similar variation in cross-reactivity with one benzodiazepine drug to another benzodiazepine drug. Similarly, for the benzodiazepine immunoassay where oxazepam is the principal drug used in the formulation, testing for lorazepam and clonazepam has very poor cross-reactivity and may give false negative results for these drugs. For the end result, all laboratory-based immunoassays and POCT strips or cups have the same limitations and can provide similar misleading results. However, single-drug assays, like marijuana, cocaine, amphetamine, methamphetamine, and phencyclidine, are mostly reliable for immunoassay detection, and it may be best and economical to screen patients for illicit drug use.

In addition, POCT and analyzer have poor selectivity and also give false positive results (see [Fig. 1](#)). All these immunoassays are FDA 510K cleared for screening specific drugs in the urine at the specified cutoff in the package insert. Another caveat with laboratory-based immunoassay is in lowering the cutoff from the FDA 510K–cleared cutoffs. The FDA 510K–cleared cutoffs are based on the performance of the assay at the cutoff, and it has to meet 98% or better confidence in calling a drug negative or positive. However, the same assay may provide enough information to suspect some activity for the drug below the FDA 510K cleared cutoff, and one can then use definitive testing technology (GC-MS and LC-MS/MS) to further confirm the presence or absence of drugs. Although there are a few non-FDA 510K–cleared assays in many clinical laboratories, full caution must be taken in developing and validating these assays based on the laboratory-based test regulations. Whether FDA 510K cleared or laboratory developed, it should be understood that POCT and analyzer results are presumptive and that GC-MS and LC-MS/MS are “definitive” testing technologies.

The GC-MS and the LC-MS/MS are highly sophisticated analytical technologies for the analysis of organic compounds in trace amounts. The LC-MS/MS revolutionized diagnostic testing. The GC-MS testing requires extensive sample cleanup and derivatization before analysis, and the GC-MS technology is not amicable to analyzing many drugs in one injection. The modern LC-MS/MS technology allows changing the mobile phase during a run, and this gives the capability of analyzing multiple similar compounds in one injection. The LC-MS/MS uses 3 technologies in one instrument. First, the high-pressure LC separates the compound by changing the mobile phase; second, the MS filters the masses based on the molecular weight and charge; third, the molecules are fragmented, and the fragments are measured for each drug and their metabolites. Each sample could take 2 to 15 minutes on the LC-MS/MS, and the analysis time depends on the number of compounds. Typically, fewer compounds take less time, and many compounds need a longer time of analysis to achieve chromatographic separation and an adequate mass spectral scan. An isotopic deuterium–labeled internal standard is used to validate the presence of each of the compounds tested. Whether quantitative or qualitative, the LC-MS/MS test is a definitive test for drugs and their metabolites by measuring the molecular weight and their fragmentations along with the chromatographic retention time, thus providing a unique molecular fingerprint for the analyte being assessed. The biological specimens have to be hydrolyzed and cleaned up before injecting into the LC-MS/MS to minimize the matrix effect. The LC-MS/MS method of development and analysis involves a high level of technology expertise and skill. The resource requirements such as GC-MS or LC-MS/MS instrumentation, technical expertise, cost, and the time that it takes to perform qualitative or quantitative testing by LC-MS/MS (definitive testing) are

considerably greater than conventional POCT and IA testing, thus justifying them as high-complexity testing methodologies.

It must be stressed that toxicology testing is to be used as an objective ancillary test for the clinical provider. For example, a patient on oxycodone may be ingesting as prescribed and/or “pill scraping” directly into the urine. In such a case, the patient with oxycodone as well as the presence of its metabolites oxymorphone (in addition to noroxycodone and noroxymorphone) in the urine is consistent with oxycodone ingestion, whereas an elevated oxycodone urine concentration and no oxycodone metabolites (oxymorphone or noroxycodone) may alert the physician that the patient may not have taken the pill as prescribed; rather, the patient scraped the pill into his/her urine. However, it could also be that the patient recently ingested the oxycodone and did not yet convert the parent drug into the metabolites. In such a case, noting the time of ingestion with serial toxicology testing (both scheduled and unscheduled) would help the clinician determine the likelihood of compliance versus diversion. It can be more difficult where prescription drugs like M and its metabolite HM are both individually prescribed pharmaceutical opiate drugs because both drugs would appear in urine. Furthermore, for some illicit drugs, concentration may not have much clinical value.

Clinical drug testing laboratories are under CLIA (Clinical Laboratory Improvement Amendments) guidance, which has no set standards for methodologies and laboratory protocols, and there is no FDA oversight on the Laboratory Developed Tests (LDT). The FDA has a proposal for the oversight of LDT assays, which is not in effect today. The certifying agencies such as the College of American Pathologists or COLA do not have guidelines for best practices in clinical drug testing and their inspection checklist is to verify the CLIA requirement. Therefore, some clinical laboratories may screen by immunoassay and confirm the positive results on GC-MS or LC-MS/MS, whereas other laboratories may perform the definitive test on LC-MS/MS at detection levels without using the immunoassay screening. The clinical laboratories performing the immunoassay screen first and reflexing to LC-MS/MS or GC-MS confirmation are using the SAMHSA (The Substance Abuse and Mental Health Services Administration) model. This laboratory protocol is more economical; however, this misses many psychoactive drugs (SAMSHA Household Survey List) in the patient specimen. There are 3 reasons for this: (1) the POCT and analyzer do not cross-react with all the drugs in a class of druglike opiates and benzodiazepines; (2) the analyzer and the POCT have high cutoffs and miss low concentrations; (3) not all the psychoactive drugs have commercial POCT and analyzer reagent kits and these laboratories are not including these drugs in their test menu. Therefore, definitive testing by LC-MS/MS whether qualitative or quantitative may be the best practice protocol in pain and addiction testing to screen for all the opiates, opioids, benzodiazepines, stimulants, and sedatives. Nonetheless, analyzer or POCT can provide a very economical way to screen for illicit drugs like marijuana, cocaine and methamphetamine.

Specimen Validity Test

Specimen validity is very important in the detection process for the evaluation of drug use for proper diagnosis and treatment.³³ Oral fluid, hair, and blood are direct-observed collection. Urine specimens are subject to adulteration or substitution. There are many adulterants available on the Internet to beat the drug test. Most of them are oxidants to interfere with immunoassay test. Some of these oxidants change the structure of the marijuana metabolite and make it undetectable by immunoassay and LC-MS/MS. The characteristics of the urine specimen are based on its appearance, temperature, pH, creatinine concentration, and specific gravity. Normal urine has a temperature of 90°F to 100°F and a pH between 4.5 and 8.1. Urine specimens

at room temperature may increase the pH due to micro-organism growth. Normal urine has a creatinine concentration of 20 mg/dL or higher and specific gravity greater than 1.003. It is also known that patients may bring someone else's urine to avoid drug detection. Therefore, observed urine collection is the best practice.

SUMMARY

Pain management continues to pose a challenge to the clinician who walks the tight-rope of providing appropriate pain relief while also monitoring the signs and potential for abuse and diversion. Although the relationship of the clinician and patient remains paramount for appropriate trust and management in this regard, appropriate utilization of toxicology testing provides an objective measure of ancillary support to facilitate such management. Understanding when to test, how often, and which fluids to sample, in addition to the variability and differences in methodology, as well as human physiologic variability can help the clinician with respect to testing approaches and interpretation for effective pain management.

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