A Practical Guide to Urine Drug Monitoring

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Urine drug monitoring is an important tool for substance misuse or abuse and adherence to a prescribed regimen.

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Urine drug monitoring (UDM) is an important tool to screen adherence and identify possible misuse and abuse in patients on opioid therapy.[1] Various guidelines for opioid therapy emphasize the importance of UDM as a standard of care.[2-6] Routine and random monitoring is recommended for all patients on long-term opioid therapy prior to initiation and throughout duration of therapy.[1-3] The recommended UDM frequency varies based on individual risk assessment and clinical judgment. Similar to any other diagnostic or monitoring test, the goal for UDM should be to guide therapy and improve patient care (Box). Inappropriate interpretation of the results and failure to order definitive testing when necessary may adversely affect patient care.

General Principles for Urine Drug Monitoring

1. Discuss with patients prior to initiation of therapy that UDM is routine monitoring conducted for their safety and for public safety.

2. Obtain a comprehensive and full medication history, including herbals and over-the-counter supplements and medications due to potential cross-reactivity and false positives.

3. Ask patients how they are taking their medications and time of their last dose. For example, patients prescribed an opioid analgesic for "as needed use" might be expected test negative for the prescribed opioid.

4. Do not make decisions that alter treatment plan without seeking definitive testing if indicated.

5. Discuss the test results with patients and address aberrant drug behavior. Sending the patient a letter in the mail with test results and discharging the patient from the clinic is not appropriate and could increase risk for substance misuse.

URINE DRUG MONITORING

Sample Collection

Urine drug testing generally requires a minimum of 30 mL of urine (depending on the kit type) collected in a private restroom. In the authors' experience, the sample collection most often is unobserved in clinical practice. Most laboratories keep urine samples for a limited time, often 7 days. Therefor, if results are unexpected, health care providers must notify the laboratory in a timely manner to order definitive testing if indicated.

Specimen Validity Testing

Attempts to dilute, adulterate, and substitute urine may be detected by visual inspection and laboratory validity testing. Validity testing of urine specimens includes temperature, specific gravity, pH, urine creatinine, and presence of adulterants (Tables 1 and 2).[7-9] Urine temperature within 4 minutes of voiding should range from 90°F to 100°F in a healthy individual, whereas temperatures outside of this range may suggest a substituted specimen has been provided. Many specimen cups have a temperature gauge on the side of the cup. A specimen outside of the physiological range should be recollected.

The combination of specific gravity and urinary creatinine may help screen for dilution or substitution. Dilution may occur precollection by consumption of excess amounts of fluids or postcollection by adding fluid to the specimen. Other causes of diluted

urine should be considered, such as renal tubular dysfunction or diuretic use. Household adulterants include vinegar, detergent, sodium chloride, hydrogen peroxide, eye/nose drops, soda, or ammonia.[10] There are numerous commercially available adulterants, including Klear, UrinAid, Urine Luck, Stealth Synthetics, Whizzies, and Clear Choice. The active ingredients of some include peroxide/peroxidase, sodium or potassium nitrate, pyridinium chlorochromate, or glutaraldehyde. There are laboratory tests to detect the presence of these adulterants. Whenever in doubt, it is advisable that health care providers (HCPs) contact their laboratory to investigate tampering. Another approach if tampering is suspected is to collect blood samples. Although this method is more expensive and invasive, it eliminates means of tampering. Hair follicle testing is an option as well.

TYPES OF URINE DRUG MONITORING

There are 2 general types of UDM: Presumptive by immunoassay (IA) and confirmatory testing by chromatography. Simply, UDM by IA commonly referred to as urine drug screening (UDS), serves as the differential assessments, whereas chromatography is the definitive assessment. This article reviews the clinical utility and limitations of the 2 types of UDM, including false positives and false negatives, and when to order more tests.

Immunoassay

The IA drug test uses antibodies to detect the presence of selected drugs and/or their metabolites based on a predetermined cutoff threshold.[8] Immunoassay monitoring is the initial qualitative test to identify the presence of drug classes in the urine based on a detection threshold. Typically, UDM by IA is performed as an initial evaluation of potential appropriate use, misuse, nonuse, or abuse of medications. It also can detect the presence of illegal substances or unprescribed medications. Immunoassay is relatively quick, inexpensive, and sensitive; however, because it lacks specificity, it can result in various false positives and false negatives.

Immunoassay tests also are subject to varying windows of detection depending on the substance ingested (Table 3). Most automated IAs include the "Federal Five" drugs or drug classes tested for in federal employees, which include marijuana, cocaine, opiates, amphetamines, and phencyclidine (PCP).[8,9] Additional tests may be ordered separately or electronically built into the ordering system for other drugs or drug classes, such as benzodiazepines, barbiturates, lysergic acid diethylamide (LSD), propoxyphene, buprenorphine, tramadol, methadone, fentanyl, and oxycodone.[4]

The cutoff levels listed in Table 1 are consistent with testing for employment but not necessarily for aberrant behavior in patients receiving long-term opioid therapy. These cutoffs lower the risk of false positives and provide better accuracy with clinical monitoring. For example, a level of 2,000 ng/mL is listed for both test types in Table 4, but for clinical testing, the IA cutoff is 3,000 ng/mL, and gas chromatography/mass spectrometry (GC-MS) can detect even trace amounts of opioid and their metabolites. Clinicians

TABLE 1 Characteristics of Valid Urine Specimen[7-9]

Characteristics	Normal Range
Creatinine, mg/dL	20-400
Specific gravity	1.002-1.030
pH	4.5-8.0
Temperature, within 4 minutes of voiding, °F	90-100

TABLE 2 Dilution, Adulteration, Substitution of Urine Specimen[7-9]

Urine States	Description
Diluted	Urine creatinine ≥ 2 mg/dL but < 20 mg/dL Specific gravity > 1.001 but < 1.003
Substituted	Urine creatinine < 2 mg /dL Specific gravity < 1.001 or > 1.020
Adulterated	pH < 3 or > 11 Nitrite concentration > 500 mcg/mL Chromium concentration > 50 mcg/mL Presence of: Halogen (bleach, iodine, fluoride), glutaraldehyde, pyridine, surfactant

TABLE 3 Detection Window for Selected Drugs in Urine

Drug	Time After Ingestion
Alcohol	7-12 h
Amphetamines	2-3 d
Benzodiazepines	
Short acting	2 d
Intermediate acting	5 d
Long acting	10-30 d
Cannabinoids	
Single use	3 d
Moderate use (4x/wk)	5-7 d
Daily use	10-14 d
Chronic heavy use	≥ 30 d
Cocaine metabolites	
20 mg IV cocaine	< 1.5 d
Chronic use	2-3 d (up to 7 d at high doses)
Opioids	
Codeine	2 d
Heroin (morphine)	2 d
Hydrocodone	2-3 d
Hydromorphone	2-3 d
Methadone	3-5 d
Oxycodone	2-4 d
Phencyclidine	8 d

TABLE 4 Federal Five Panel Cutoffs

Analyte	Initial Immunoassay Test Level, ng/mL	Confirmatory GC-MS Test Level, ng/mL
Opiates	2,000	2,000
Cannabinoid	50	15
Amphetamine	500	250
Cocaine	300	150
Phencyclidine	25	25

Abbreviation: GC-MS, gas chromatography–mass spectrometry.

must be familiar with the available tests at their institution. Most commonly when monitoring patients that are prescribed pain medications, the IA panel includes the Federal Five plus benzodiazepines, barbiturates, and often methadone as well.

The opiate panel with IA tests for opium alkaloids and/or their metabolites, including morphine and codeine.[7-9] Heroin is a semisynthetic opioid that is metabolized to diacetyl morphine and ultimately is detected as morphine.[7,8] Other semisynthetic opioids, such as hydrocodone and oxycodone, may or may not be detected by the opiate IA depending on the dose and assay. Synthetic opioids, such as fentanyl, methadone, or meperidine, are not detected by the opiate IA and need to be ordered separately. Table 5 shows opioid classes and their ability to be detected by IA. Clinicians should be familiar with their laboratory assay and know which test needs to be ordered.

Benzodiazepine IAs often are designed to detect nordiazepam, oxazepam, and temazepam, all of which are metabolites of diazepam. However, benzodiazepine IAs also can detect other drugs that are structurally similar to benzodiazepines.[11,12] This means that benzodiazepines are detected based on their ability to cross-react with the IA test. Lorazepam and clonazepam have low cross-reactivity and are generally not detected on benzodiazepine IA.[12,13] Therefore, it is not uncommon for patients on lorazepam or clonazepam to test negative for benzodiazepines on this IA. If these patients do test positive at low doses, it could be a concern that they are taking a different benzodiazepine instead of, or in addition to, the prescribed medication.

Amphetamines and methamphetamine are simple molecules that are difficult to develop specific antibodies for; therefore, they carry a high false-positive rate with IA testing.[8] It is important to note that methylphenidate is not detected by the amphetamine IA as it is not an amphetamine.[8] The IA for cocaine tests specifically for benzoylecgonine, a metabolite specific to cocaine and has no cross-reactivity.[8,12,14]

False positives. Due to the lack of specificity of UDM by IA, false positives are common; with the exception of cocaine. Clinicians must obtain a comprehensive medication history of the patient, including over-the-counter medications, herbals, and supplements. Table 6 lists common sources of false positives with UDM by IA.[1,8,9]

False negatives. A variety of factors can cause false-negative results, including

the cross-reactivity of the antibody in the IA, the cutoff concentration that yields a positive result, and/or the time between drug ingestion. As discussed previously, the opiate panel tests for metabolites of morphine, codeine, and heroin, which consequently may lead to semisynthetic/synthetic opioids not being detected.[8,11] For example, a patient who was prescribed hydrocodone/acetaminophen 5 mg/325 mg 4 times a day, tests negative for opiates by IA. The negative result is not unexpected because the dose of semisynthetic opioid is too low for detection by IA.

TABLE 5 Opioid Classes and Detection by Opiate Immunoassay[a]

Select Naturals (extracted from opium)	Select Semisynthetics (derived from opium sources)	Select Synthetics
Codeine	Hydrocodone	Methadone
Morphine	Oxycodone	Fentanyl
Opium	Hydromorphone Oxymorphone Buprenorphine Heroin (detected as morphine)	Meperidine Tapentadol Tramadol
Detectability by Opiate Immunoassay		
Yes	May or may not be detected depending on the lab assay and dose Buprenorphine is not detected on opiate screen	Not detected at any level by opiate immunoassay and require their own test

[a] This table contains commonly used opioids and is not meant to be cpmprehensive.

Chromatography

Chromatography generally is reserved for confirmatory or definitive testing when the initial UDM by IA results are unexpected.[1] Unlike IA, chromatography can detect the presence of specific drugs and/or metabolites. Types of chromatography testing include GC/MS, liquid chromatography tandem mass spectrometry (LC/MS/MS), and high-performance liquid chromatography.[9] Depending on the specific test, chromatography uses a gas or liquid carrier medium to separate the urine sample's compounds by their molecular interactions with the carrier medium (mainly by different polarities). During this separation process, all the individual compounds are fed into a mass spectrometer, that ionizes the compounds and detects fragments by using their mass-to-charge ratios. This process allows for the identification of distinct compounds based on their molecular fingerprints.

Gas chromatography/mass spectrometry has remained the standard test for confirmatory testing.[1,8] However, it is important to note that LC/MS/MS has been gaining favor over GC/MS. Using LC/MS/MS requires less urine volume to conduct an analysis, and the analysis has a second analytical separation step, thus it is expected to have a lower susceptibility to false results caused by concomitant use of other medications.[15,16]

Regardless of the test medium, quantitative confirmation through chromatography offers several advantages over IA. It is more accurate, as it can identify small quantities of specific drugs and confirm their presence in urine.[8] Also, although there are still cutoff limits associated with chromatography, the specific cutoffs are much lower in value than those in IA tests. Finally, a study conducted in 2010 by Pesce and colleagues found that IA testing was associated with varying rates of false-negative results compared with those of LC-MS/MS.[17] Specifically, false-negative rates associated with IA were found to be 22%, 50%, and 23.4% for benzodiazepines, cocaine, and propoxyphene, respectively.[17] Unfortunately, chromatography testing methods take longer to produce results and are costly compared with those of IA.Thus, chromatography testing methods typically are reserved for when the IA produces unexpected results. Conversely, IA can be done at point of care with in-office readable cups or strips, or sent out for a 24-hour to 48-hour turnaround time.[7,8]

Alcohol Testing

Health care providers also could screen for alcohol misuse, which can compromise safe opioid use. Alcohol can accelerate the release of certain sustained-release for-

TABLE 6 Substances Tested by Immunoassay and Agents Contributing to False-Positive Results

Substances Tested by Immunoassay	Positive Results (Brand Name)
Amphetamine and methamphetamine	Amantadine Bupropion Chlorpromazine Desipramine Ephedrine Labetalol l-methamphetamine (Vick's inhaler) Phentermine Phenylephrine Promethazine Pseudoephedrine Ranitidine Selegiline Trazodone
Benzodiazepines	Oxaprozin Sertraline Efavirenz
Methadone	Quetiapine Verapamil
Marijuana metabolites	Dronabinol (Marinol) Efavirenz Hemp-containing foods NSAIDs PPIs
Opiates	Dextromethorphan Diphenhydramine Poppy seeds Quinine Quinolones Rifampin Verapamil
Phencyclidine	Dextromethorphan Diphenhydramine Doxylamine Ibuprofen Imipramine Meperidine Thioridazine Tramadol Venlafaxine O-desmethylvenlafaxine (Pristiq)

Abbreviations: NSAID, nonsteriodal anti-inflammatory drugs; PPIs, protein pump inhibitors.

mulations, causing "dose dumping."[18] Furthermore, alcohol also can increase the risk of opioid-induced respiratory depression. Many laboratories include ethanol that is measured using an enzymatic reaction and generally detected 12 hours after alcohol use.[7-9] Urinary ethanol is not an optimal marker for assessing alcohol use. Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are 2 minor metabolites of ethanol formed by UDP-glucuronosyltransferase.[19] These markers can be detected for up to 80 hours after alcohol consumption. Markers for prolonged and/or heavy drinking include but are not limited to phosphatidylethanol, γ-glutamyltransferase, or carbohydrate-deficient transferrin.[20]

PHARMACOKINETICS/ PHARMACOGENETICS

Pharmacokinetics is what the body does with the drug and is measured by absorption, distribution, metabolism, and elimination.[16] Pharmacokinetics ultimately determines the fate of how much and how fast a drug and/or metabolites end up in the urine. It is important to understand the pharmacokinetics to interpret the results of UDM by chromatography as the reported results include parent drugs and metabolites.

Some metabolites of medications available commercially could be mistaken as if the patient were taking a medication that was not prescribed. For example, hydromorphone is a metabolite of hydrocodone and oxymorphone is a metabolite of oxycodone, both of which are commercially available as stand-alone prescriptions. Likewise, oxazepam is commercially available as is temazepam, and both are metabolites of diazepam. Also, it is important to consider patient's body habitus, which affects volume of distribution, meaning more drug is stored in the periphery and may have a longer detection window.[21] Patients with renal and/or hepatic impairment can have reduced clearance of the medications.

It is equally important to consider the role that pharmacogenetic polymorphism can play in UDM, as polymorphisms may impact results.[1,8] For example, consider a patient on extended-release oxycodone

30 mg twice daily. Oxycodone is metabolized via cytochrome (CYP) P450 enzyme 3A4 into noroxycodone and, to a much lesser extent, by CYP2D6 into oxymorphone. In this case, if tested by chromatography, the patient's urine level of oxycodone should be higher than that of either metabolite; specifically, the urine level of noroxycodone should be higher than that of oxymorphone. If there are only concentrations of oxycodone found in the urine with no metabolites, the possible explanations are either the patient dissolved oxycodone into the urine sample without ingestion or the patient may have poor activity of CYP2D6 and CYP3A4 isoenzymes; the latter of which can be confirmed by pharmacogenetic testing. Notwithstanding, drug-drug interactions with CYP inhibitors can produce the same outcome.

CONCLUSION

Urine drug monitoring is an important tool for substance misuse or abuse and adherence to the prescribed regimen. The most commonly used test is UDM by IA due to its low cost and quick results. However, it comes with an array of false-positive and false-negative results. Clinicians should seek definitive results by confirmatory testing prior to making changes that alter patient care, and all results should include discussions with the patient.

Clinical pharmacy specialists are generally an excellent and often untapped resource to provide guidance for interpretation of both IA and chromatographic testing. Clinical pharmacy specialists have an excellent understanding of the physical and medicinal chemistry properties of laboratory testing, a vast understanding of drug metabolites and interactions that might increase or decrease drug concentrations might account for possible false positives and false negatives, and they can help decipher unexpected results.

Finally, it is important to consider that UDM is done *for* patients and not *to* patients, with the ultimate goal of improving the safety of the patient and the public. Unexpected results should be discussed with patients to identify the underlying reasons, which may then warrant further intervention, such as definitive testing and ultimate referral to a substance abuse treatment program. Simply sending a discharge or medication discontinuation letter to a patient can create a confrontational situation rather than an educational opportunity for both patient and provider.

Author disclosures

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Disclaimer

References

1. Owen GT, Burton AW, Schade CM, Passik S. Urine drug testing: current recommendations and best practices. *Pain Physician.* 2012;15(3)(suppl):ES119-ES133.
2. US Department of Defense, US Department of Veteran Affairs, The Opioid Therapy for Chronic Pain Working Group. *VA/DoD clinical practice guideline for opioid therapy in chronic pain.* Version 3.0. Washington, DC: Veterans Health Administration and Department of Defense; 2017.
3. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep.* 2016;65(1):1-49.
4. Cheung CW, Qiu Q, Choi SW, Moore B, Goucke R, Irwin M. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. *Pain Physician.* 2014;17(5):401-414.
5. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.
6. Manchikanti L, Abdi S, Atluri S, et al; American Society of Interventional Pain Physicians. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 – guidance. *Pain Physician.* 2012;15(3)(suppl):S67-S116.
7. Hammet-Stabler CA, Webster LR. A clinical guide to urine drug testing. CME certified monograph. http://ccoe.rbhs.rutgers.edu/online/ARCHIVE/endurings/09MC07.pdf. Published May 2008. Accessed March 23, 2018.
8. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc.* 2008;83(1):66-76.
9. Gourlay DL, Heit HA, Caplan YH. Urine drug testing in clinical practice. The art and science of patient care. Edition 6. https://www.remitigate.com/wp-content/uploads/2015/11 /Urine-Drug-Testing-in-Clinical-Practice-Ed6_2015-08.pdf. Published August 31, 2015. Accessed March 23, 2018.
10. Jamison RL, Oliver RE. Disorders of urinary concentration

and dilution. *Am J Med.* 1982;72(2):308-322.
11. Valentine JL, Middleton R, Sparks C. Identification of urinary benzodiazepines and their metabolites: comparison of automated HPLC and GC-MS after immunoassay screening of clinical specimens. *J Anal Toxicol.* 1996;20(6):416-424.
12. Raouf M, Fudin J. Benzodiazepine Metabolism and Pharmacokinetics. http://paindr.com/wp-content/uploads/2015/10/Revised-BZD_-9-30.pdf. Published September 30, 2015. Accessed March 23, 2018.
13. DRI Benzodiazepine Assay [package insert]. Fremont, CA: Mircogenics Corp; 2012.
14. Carney S, Wolf CE, Tarnai-Moak L, Poklis A. Evaluation of two enzyme immunoassays for the detection of the cocaine metabolite benzoylecgonine in 1,398 urine specimens. *J Clin Lab Anal.* 2012;26(3):130-135.
15. Mikel C, Pesce A, West C. A tale of two drug testing technologies: GC-MS and LC-MS/MS. *Pain Physician.* 2010;13(1):91- 92.
16. Stout PR, Bynum ND, Mitchell JM, Baylor MR, Ropero-Miller JD. A comparison of the validity of gas chromatography- mass spectrometry and liquid chromatography- tandem mass spectrometry analysis of urine samples for morphine, codeine, 6-acetylmorphine, and benzoylecgonine. *J Anal Toxicol.* 2009;33(8):398-408.
17. Pesce A, Rosenthal M, West R, et al. An evaluation of the diagnostic accuracy of liquid chromatography-tandem mass spectroscopy versus immunoassay drug testing in pain patients. *Pain Physician.* 2010;13(3):273-281.
18. Gudin J, Mogali S, Jones J, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013;125(4):115–130.
19. Böttcher M, Beck O, Helander A. Evaluation of a new immunoassay for urinary ethyl glucuronide testing. *Alcohol Alcohol.* 2008;43(1):46-48.
20. Peterson K. Biomarkers for alcohol use and abuse—a summary. *Alcohol Res Health.* 2004-2005;28(1):30-37.
21. Sera LC, McPherson ML.Pharmacokinetics and pharmacodynamic changes associated with aging and implications for drug therapy. *Clin Geriatr Med.* 2012;28(2):273-286.