

The Role of Urine Drug Testing In Chronic Pain Management: 2013 Update

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“Trust but verify” is good advice in many life situations. When administering opioids for chronic pain, verification is vital to successful therapy and patient safety. This is because studies show discrepancies between medical direction and actual medication-regimen adherence among patients on opioid therapy.¹⁻³



Of 470 patients treated in an urban pain management setting, 45% were found retrospectively to have inconsistent urine screens, defined as the absence of a prescribed opioid, the presence of illicit substances or unauthorized prescription medications, or an adulterated urine sample.¹ Furthermore, research has shown that physicians are easily fooled

by actors posing as patients.⁴ Some nonadherence may be unintentional, and some may reflect serious problems with use that stem from causes such as abuse, addiction, diversion for illegal sale, or inappropriate use due to mental health comorbidities or life stress.

Urine drug monitoring (UDM) can help inform clinical decisions. Although a valuable

Table 1. Types of Urine Drug Monitoring

Urine Drug Screening (UDS)	Urine Drug Testing (UDT)
Immunoassay screen	GC-MS or LC-MS/MS
In-office, point-of-care or lab-based test	Laboratory, highly specific and sensitive
Results within minutes	Results in hours or days
Detects drug classes and a few medications, illicit substances	Measures concentrations of all medications, illicit substances and metabolites
Guidance for preliminary treatment decisions	Definitive identification and analysis
Cross-reactivity common: more false positives	False-positive results rare
Higher cutoff levels: more false negatives	False-negative results rare

GC-MS, gas chromatography-mass spectrometry; **LC-MS/MS**, liquid chromatography-tandem mass spectrometry

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tool, UDM cannot be used as a sole determinant of adherence, and its benefits and limitations should be clearly understood by physicians and other prescribing clinicians.⁵ Most evidence suggests that UDM is best used in concert with other clinical monitoring tools, such as checks of the state prescription database and ongoing assessments of the patient's pain relief, function, quality of life, risk stratification for potential misuse, and psychosocial indicators.

Need for Better Medication Management In Chronic Pain

A wide prevalence of chronic pain in the United States is shown in a recent report from the Institute of Medicine (IOM), that found more than 100 million individuals reporting chronic pain,⁶ costing up to \$635 billion annually in medical treatment and lost productivity.⁷ Few of these people will need long-term opioid therapy, but certain patients whose pain is severe enough and who have not responded to earlier interventions do achieve meaningful pain relief in the long term.⁸ For these patients, initial assessment and ongoing monitoring of progress toward clinical goals are necessary. Poor adherence puts patients at risk for overuse or underuse of medication, and also puts the public at risk for increased availability of opioids to abuse through diversion. Federal statistics show that most opioids diverted for nonmedical use came from home medicine cabinets. Data from the National Survey on Drug Use and Health (2010-2011) showed that 70% of the United States' 2.3 million first-time prescription drug abusers got the drugs from family and friends.⁹ There are clinical and societal consequences when opioids are misdirected away from their medical purpose and end up in the wrong hands.

Reasons for Urine Drug Monitoring

For pretreatment assessment and regular ongoing monitoring, UDM is relatively quick and easy to perform. UDM can help:

- assist with diagnosis and therapeutic decision making;
- corroborate and document the patient's self-report of adherence;
- detect the presence of prescribed medication as evidence of regimen adherence (absence may indicate diversion or hoarding, although caution must be used in drawing conclusions due to test limitations);
- identify unauthorized substances, whether illicit street drugs or nonprescribed medications (signs of drug misuse, abuse, or possible addiction)
- provide scientific data that a clinician can use to assess patient medication management related to individual metabolism, drug-drug interactions, and substance use disorders; and
- provide documentation for the patient for workplace or legal requirements.

Patients Who Would Benefit From Urine Drug Monitoring

Most patients to be initiated on chronic opioid therapy should have an initial urine screen in keeping with "universal precautions," which is modeled on the infectious disease paradigm.¹⁰ Periodic follow-up testing is recommended. In addition to the clinical utility of UDM for medication management, certain patient characteristics observed clinically suggest the need for adherence testing and include aberrant drug-seeking behavior, refusal of a full diagnostic workup, and substance abuse history. However, consensus guidelines on opioid prescribing jointly endorsed by

the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) state that patient risk factors can be poor predictors of adherence, leading to missed problematic behavior by other patients.¹¹ The APS/AAPM guidelines recommend random as opposed to scheduled testing as a better measure of true patient behavior.

Clinical Value of Testing

Monitoring for management of medications and regimen adherence in patients receiving opioid therapy should be an expected part of therapy. This monitoring is comparable to checking for the effects of medications to regulate diabetes, cardiovascular irregularities, and other chronic medical conditions.

Although evidence is lacking for improved clinical outcomes with UDM, it is apparent that the presence of unauthorized substances or the absence of prescribed ones could point to problems that would interfere with safe and effective opioid therapy.¹¹ Using several monitoring measures together may be best. One study showed that 45% of patients with previously demonstrated aberrant drug-related behaviors were able to adhere to their medication regimens after management with UDM in combination with signed treatment agreements and multispecialty care.¹²

We must remember that there is a difference between prescribing a blood pressure medication and a potentially rewarding drug, such as an opioid, in which public health issues are considered as well as individual patient welfare. Because UDM is now an expected standard of practice in pain management, failure to perform the test could lead to regulatory or legal sanctions.

Issues in Testing

USE OF PATIENT AGREEMENTS

Treatment agreements to lay out the goals, expectations, responsibilities, and parameters of the selected course of therapy can be useful¹⁰ and, if used, should be signed by the provider and the patient. Up-front agreements can reduce the stigma of UDM that exists in some patients' minds and make clear that adherence monitoring is a routine part of medical practice. As mentioned, UDM can be explained as being similar to any other chronic disease-monitoring test and as a tool to help the clinician manage medications and help the patient better understand his or her condition.

TYPES OF TESTS

In contrast to forensic testing, which is concerned with locating illegal use of substances, clinical testing seeks to provide scientific data to help clinicians effectively manage patient medication therapy and establish adherence. For that reason, 2 types of tests are usually necessary: urine drug screening (UDS) and urine drug testing (UDT) (Table 1).

Urine drug screening is an immunoassay qualitative test that detects whether a drug class is present and, in some instances, tests for a few specific drugs. This radioactive or enzyme-mediated immunoassay test can show whether or not certain drug classes are present but typically cannot isolate specific opioids or identify whether more than one drug in a drug class is present.¹³ This step is done at the point of care (POC).

If the UDS returns unexpected results, UDT can be used. This laboratory test may include 1 or 2 steps. Some labs require a first step of qualitative immunoassay testing that confirms the POC test and indicates if a drug class is present ahead of the second step of quantitative testing, which identifies all drugs present in a drug class and their metabolites. Other labs do not require the lab qualitative immunoassay and proceed directly to lab quantitative testing for all drugs and metabolites ordered by the clinician. Lab quantitative testing is done via high-performance liquid chromatography or combination techniques, such as gas chromatography–mass spectrometry or liquid chromatography–tandem mass spectrometry (LC-MS/MS), which are far more specific than immunoassay, and can detect actual molecular structures of specific drugs and their metabolites.¹³

CHOICE AND TIMING OF TESTS

Some thought must be given to when specific tests are necessary. Immunoassay POC tests are administered outside of laboratory settings and are read visually by clinic personnel.¹³ Offering quick turnaround, they are used for initial screening only, and clinicians should not make critical clinical decisions based on these results. Clinic staff must be trained to follow precisely all protocols established by the manufacturer of the test. Each POC test package insert will list specific drugs that the test will not identify and common cross-reactivity that may give a false negative or a false positive; therefore, reading the package insert is critical to true test results. Test accuracy and cutoff scores vary, and it is recommended that positive results be sent for lab confirmation/quantification before making therapeutic decisions based on results.

Traditionally, UDS has screened for amphetamines, cocaine, opiates, marijuana, and phencyclidine based on the forensic testing process.¹⁴ A clinical approach to testing now reflects common drugs and most drugs prescribed for pain. If UDS returns a positive or otherwise unexpected result, UDT should follow to identify what molecules exist and their concentrations. Based on patient risk stratification, drug use history, presence or absence of aberrant behaviors, or individual clinical assessments, UDT (ie, quantitative testing) may be ordered as the first step.

Specific opioids to test for may include buprenorphine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone.

Table 2. Validity Testing of a Urine Specimen¹⁵⁻¹⁶

Urine specimen is reported as:	When:
Diluted	Creatinine concentration ≥ 2 mg/dL but < 20 mg/dL, and specific gravity > 1.001 but < 1.003
Substituted	Creatinine concentration < 2 mg/dL and specific gravity ≤ 1.001 or ≥ 1.020
Adulterated	pH < 3 or ≥ 11 ; nitrite concentration ≥ 500 Qg/mL; chromium (VI) concentration ≥ 50 Qg/mL; presence of a halogen (eg, from bleach, iodine, fluoride), glutaraldehyde, pyridine, or surfactant

Depending on the patient’s medication profile—which may include medications for comorbid conditions, such as anxiety, depression, or sleeplessness—if mixed with opioids, could increase safety risks or cause serious side effects, a clinician may choose to include these adjuvant medications when testing. These medications may include benzodiazepines, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, anxiolytics, sleep medications, and other substances as deemed appropriate by the clinician.

SPECIMEN ADULTERATION VALIDITY TESTING

Patients may tamper with urine samples to hide aberrant behaviors by adding adulterants, diluting the sample, or substituting another individual’s sample for their own; or they may attempt to influence test outcome by ingesting excessive water or diuretics prior to giving a sample.¹³ Testers should record the temperature of urine within 4 minutes of voiding, with temperatures outside the range of 90°F to 100°F suggesting substitution. Three tests of specimen validity with federally mandated criteria for interpretation are for urinary creatinine, specific gravity, and pH (Table 2).¹⁵⁻¹⁶ For comparison, know that a randomly collected adult urine sample (with some exceptions) should:

- contain 15 to 400 mg/dL of creatinine,
- have a specific gravity of 1.002 to 1.030, and
- have a pH in the range of 4.5 to 8.0.73.

In addition, laboratory adulteration testing may identify urine alteration that is not possible to detect with POC testing.

CUTOFF SCORES AND OTHER TEST INFORMATION

Various testing methods have different cutoff levels, which reflect the concentration necessary for detection of that substance. Immunoassay results will be reported using terms that indicate only whether a substance is present. In some instances, the drug may be present but the level is too low to be read as positive. The cutoff levels for lab quantitative testing are reported in ng/mL concentration and are generally much lower than those of immunoassay tests, allowing for detection at

clinically relevant levels. Clinicians should communicate with labs to ensure reporting methods are consistent with the needs of clinical practice and be aware of the cutoff levels used by their lab of choice.

Interpreting Urine Drug Monitoring Results

The most important limitation to understand is that a UDM result cannot determine exposure time, dose, or frequency of drug use, and certainly cannot be used to diagnose addiction. Test results should not in themselves dictate therapeutic decisions, but must be interpreted in the context of additional clinical signs and be discussed with the patient.

When interpreting test results, physicians should consider the possibility of false negatives or false positives as influenced by testing methods, known cross-reactivity of immunoassays, opioid drug metabolism, pharmacogenetic variations, pharmacokinetics, and other factors. A false negative occurs when a drug is actually present but the test returns a result below the cutoff value or does not detect that particular analyte. A false positive indicates that a substance is present when it is not. Immunoassay test results return close to 50% false results depending on the drug class, whereas with LC-MS/MS quantitative lab testing, false results are far more rare.¹⁷

Factors that could give rise to false negatives or false positives include the following:

Cross-reactivity, which is possible with foods, over-the-counter (OTC) medications, and prescribed drugs.¹³ A well-known false-positive result is possible for opiates with the ingestion of poppy seeds, depending on the test method cutoff value. Table 3 lists that and other substances reported to cause false-positive results. To avoid false positives, consider informing lab personnel of all prescribed and OTC medications that a patient is taking that could interfere with interpretation. It is also recommended that clinicians work with clinical labs that have toxicologists and clinical pharmacists available 7 days a week for consultation, when trying to interpret lab results.

Limited windows of detection. Most drugs can be detected via UDM for 2 to 3 days after exposure.¹⁸

Table 3. Possible False-Positive Results¹³

Substance Ingested	Possible False Result
Poppy seeds	Opiates
Quinolones (antibiotics)	Opiates
Quetiapine (antipsychotic)	Methadone
Trazodone (antidepressant)	Fentanyl
Venlafaxine (antidepressant)	Phencyclidine
Clobenzorex (diet pill)	Amphetamine
Fenproporex (diet pill)	Amphetamine
Promethazine (for allergies, agitation, nausea, and vomiting)	Amphetamine
<i>l</i> -methamphetamine OTC nasal inhaler	Amphetamine

OTC, over the counter

However, misunderstood dosing directions and the rate at which an individual metabolizes opioids due to genetic factors can influence results.

Lab error or test insensitivity. Some immunoassays are not sufficiently sensitive to detect a drug at a given level, particularly opioids at therapeutic levels. If a result is inconsistent with the clinical picture, confirm with the lab that its assays can detect the drug in question and be sure they are using the most sensitive method for that test.

Another anomaly of testing involves unexpected substances that may be present as metabolites of the prescribed drug or even by-products of the manufacturing process (Figure).¹⁹

Some examples are^{14,19}:

- codeine is metabolized to morphine;
- morphine is not metabolized to codeine, but small amounts of codeine may be a manufacturing by-product;
- codeine is partially metabolized to hydrocodone;
- hydrocodone is metabolized to hydromorphone;
- morphine can produce the minor metabolite hydromorphone; and
- heroin is metabolized to 6-monoacetylmorphine and morphine.

To help avoid errors in interpretation:

- take a complete history of all medications and other substance use before administering the test;
- be familiar with the metabolites common to opioid metabolism;

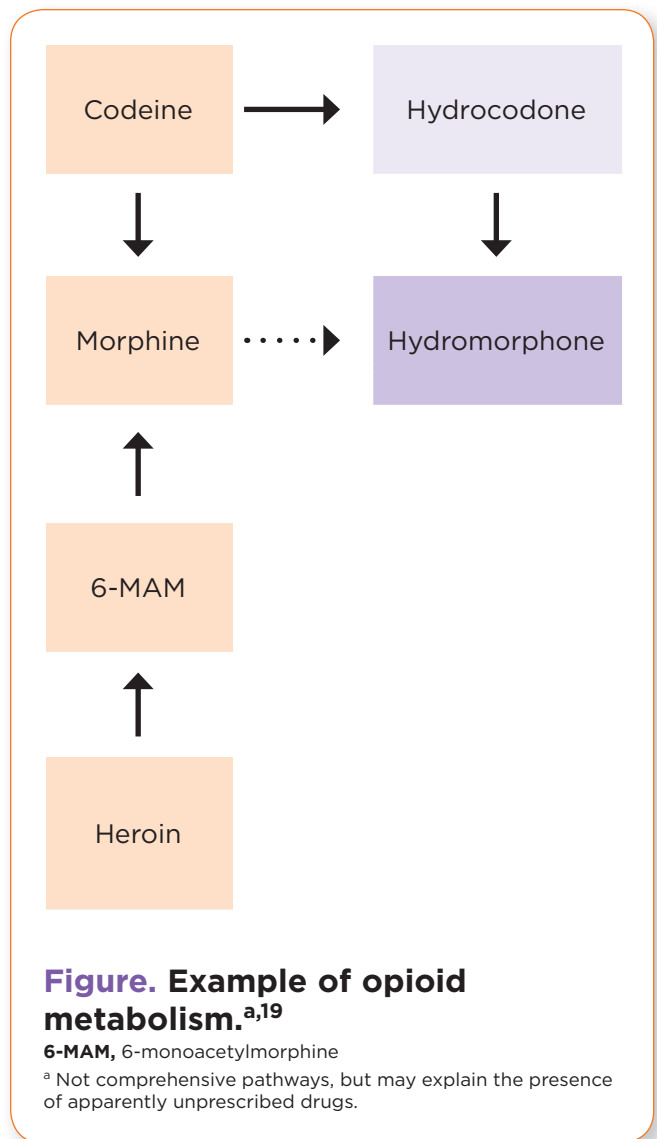


Figure. Example of opioid metabolism.^{a,19}

6-MAM, 6-monoacetylmorphine

^a Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs.

- understand that the absence of prescribed opioids does not in itself prove diversion, hoarding, or bingeing; and
- consult with your lab's toxicologist and clinical pharmacist.

Documentation

As with any other diagnostic test used to manage chronic illness, UDM should be well documented. Documentation in the medical record should include the reason the test was performed (eg, assess medication metabolism, chronic opioid therapy adherence monitoring, suspicion of other nonprescribed drug use, etc), the test results, and how the results were used in clinical care. Some examples of the latter include:

- the patient's UDM results are as expected, and the current medications will be continued;
- an unexpected, nonprescribed medication is found, the result is discussed with the patient, monitoring is

increased, prescriptions are made on a weekly basis, and the treatment agreement is reviewed; and

- tetrahydrocannabinol levels are dropping, which is indicative of a patient stopping marijuana use; monitoring is continued for 30 days beyond the detection window to ensure that none is present, and the patient is returned to a routine testing schedule.

Conclusions

Adherence testing with UDM is part of the ongoing monitoring process of patients with the disease of chronic pain who are on opioid therapy. Urine testing provides scientific information that a clinician can use to assess patient medication management in relation to individual metabolism and drug-drug interactions, confirm the presence of prescribed medications, and detect the presence of unauthorized substances. False negatives and false positives are possible with certain in-office test methods, but laboratory testing is far more accurate.

Being widely available, UDM is considered a valuable tool to track progress toward treatment goals and to guard against nonmedical use and diversion. However, to optimize the value of testing and patient outcomes, clinicians should be aware of testing issues that include differences in individual drug metabolism, the benefits and limitations of various test methods, and the nuances of interpretation. Test results can be used to improve patient care and provide valuable clinical information; however, critical clinical decisions should only be made based on the most accurate test method. All urine test results should be part of a broader risk assessment and ongoing monitoring strategy, documented in the medical record and discussed with the patient.

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