

Review Article

Urine Drug Testing in Pain Medicine

Howard A. Heit, MD, FACP, FASAM and Douglas L. Gourlay, MD, MSc, FRCPC, FASAM

Department of Medicine (H.A.H.), Georgetown University School of Medicine, Washington, D.C., USA, Departments of Psychiatry and Anesthesiology (D.L.G.), The Wasser Pain Management Center, Mount Sinai Hospital, and The Addiction Medicine Clinic, Center for Addiction and Mental Health, Toronto, Ontario, Canada

Abstract

The use of urine drug testing (UDT) has increased over recent years. UDT results have traditionally been used in legal proceedings under supervision of a medical review officer (MRO). In this context, testing has been required by statute or regulation and so is typically not in the "donor's" interest. Physicians, however, can use UDT to assist in monitoring their patient's treatment plan. By using UDT in a patient-centered fashion, both patient and physician interests are maintained. The MRO-based model of testing in the clinical setting can lead to mistrust and a deterioration of the doctor-patient relationship. Clinical testing can enhance the doctor-patient relationship when the results are used to improve communication. A patient-centered model of UDT should be used to improve quality of care. This article discusses why urine is the biological specimen of choice for drug testing; who, when and why to test; testing methods; and, most importantly, interpretation of results. J Pain Symptom Manage 2004;27:260-267. © 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Urine drug testing, chronic pain, addiction, forensic testing, compliance testing

Introduction

Urine drug testing (UDT) is a useful diagnostic tool in a number of medical disciplines, including pain management and addiction medicine. It also can be useful in the primary care setting. When used in a therapeutic model of patient-centered care, UDT provides valuable information to assist the practitioner in diagnostic and therapeutic decision making around a number of issues.

A study that audited medical records to assess the management of chronic pain patients in family practices found that only 8% of physicians utilized UDTs.¹ UDTs are used infrequently in the tertiary care oncology center.² In the authors' experience, the use of UDTs in a non-cancer pain practice is more common but sometimes is utilized in a punitive manner to "catch" the patient with an inappropriate positive or negative UDT and dismiss the patient from the practice.

While drug testing can be used in a variety of ways, it is most commonly used for two quite different purposes: to identify substances that should not be present in the urine (i.e., forensic testing) and to detect the presence of prescribed medications (compliance testing). In

Address reprint requests to: Howard A. Heit, MD, 8316 Arlington Blvd., Suite 232, Fairfax, VA 22031, USA.

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the forensic setting, the system is designed to detect a relatively small number of drug misusers in a test population consisting largely of drug-free individuals. The ultimate goal of forensic testing is to produce results that can be used, if necessary, in a court of law. When this paradigm is applied to the clinical setting, an adversarial environment may result that could harm the doctor-patient relationship.

In the case of compliance testing in a pain practice, the doctor is looking for the presence of prescribed medications as evidence of their use. Positive results are reassuring to both the patient and doctor, indicating compliance with the agreed-upon treatment plan. In compliance testing, not finding the prescribed drug or finding unprescribed or illicit drugs are disconcerting and certainly merits further discussion with the patient. For example, laboratory error and test insensitivity can result in the lab reporting absence of the prescribed drug. Even bingeing by the patient can result in unexpected negative urine reports if the patient runs out of medication prior to sample collection. Therefore, these results by themselves cannot be relied upon to prove drug diversion and are also consistent with addiction, pseudoaddiction, or the use of an opioid for non-pain purposes—so called “chemical coping.”³

Self-report of unprescribed or illicit drug use including alcohol is, however, fraught with problems.⁴⁻⁶ Pain patients may be hesitant to reveal a past or current history of drug misuse or addiction, feeling that this might disqualify them from treatment of their chronic pain. While physicians are the professionals most often cited by patients and families as the “most appropriate” source of advice and guidance about issues related to the use of alcohol, tobacco, and other drugs, they are also reported to be the “least helpful” in actually addressing these issues.⁷ It takes time to establish effective communication, mutual trust and honesty in the therapeutic relationship. Substance misuse issues must be identified and managed for effective management of medical problems.⁸

Recently, the U.S. Supreme Court (Board of Education v. Earls No. 01-332) has ruled that widespread UDT could be performed in public schools. Substance misuse in adolescent and young adults contributes to the three leading causes of mortality due to injury, homicide and suicide.⁹ Even though a positive result on a UDT

cannot measure functional impairment, in part because it does not represent drug concentration in the brain, the association between drug misuse and trauma is well established.^{9,10} The importance of appropriate drug testing and interpretation of results by primary care practitioners will only increase in years to come.

The purpose of the UDT should be explained to the patient at the initial evaluation. The UDT should be used, like all other diagnostic tests, to improve patient care.¹¹ The UDT can enhance the relationship between the doctor and patient by providing documentation of adherence to mutually agreed-upon treatment plans. This allows the doctor to be a more effective advocate on behalf of the patient with his or her family, workplace and other third-party interests. The UDT is an objective diagnostic test that is part of the medical record for the treatment of the subjective complaint of pain.

In cases in which the urine sample is inappropriately positive for unprescribed or illicit substances, this will aid in the assessment and diagnosis of drug misuse or addiction. UDT results can be used to encourage change to more functional behavior while supporting positive changes previously made. Thus, the appropriate use of a UDT result requires documentation in the medical record, and an understanding of how the results are to be used.²

In the pain management setting, the presence of an illicit or unprescribed drug must not negate the patient’s complaints of pain, but may suggest a concurrent disorder, such as addiction, that will frustrate the effective management of an underlying pain condition. While acute pain can be treated in a patient with an active addictive disorder, it is impossible to successfully treat a complaint of chronic pain in the face of an untreated addiction. To satisfactorily treat either condition, the patient must be willing to accept assessment and treatment of both. Thus, the diagnosis of a concurrent addictive disorder, when it exists, is vital to the successful treatment of chronic pain.

Specimen Choice

Since the 1970s, urine is the preferred biologic specimen for determining the presence or absence of most drugs.¹² This is, in part, due to the increased window of detection (1–3 days for most drugs or their metabolites⁷)

when compared to serum samples, the relatively non-invasive nature of sample collection, ease of storage and low cost of testing.

Whom to Test

Although the prevalence of addictive disorders in the pain population is unknown, it is unlikely to be less than that seen in the general population, which is often quoted as 10%.¹³ It should not be surprising that when UDT is reserved for those patients suspected of having drug-related problems, a significant number appear offended by the request. In fact, when uniformly applied, it is the exception rather than the rule that the pain patient is offended by a request for urine drug testing. Reliance on a history of addiction or aberrant behavior to trigger a UDT (i.e., reports of lost or stolen prescriptions, multiple unsanctioned dose increases) may miss a significant number of those individuals using unprescribed/illicit drugs.¹⁴ The diagnosis of the disease of addiction is made prospectively, over time. It is only by the continued evaluation of the patient that this diagnosis can be made.

The question of whom to test is made easier by having a uniform practice policy.¹⁵ By adopting a uniform policy of testing, stigma is reduced while ensuring that those persons dually diagnosed with pain and substance use disorders may receive optimal treatment. With careful explanation of the purpose of testing, any patient concerns can be easily addressed.¹¹

Testing Strategies

The physician must know which drugs to test for and by what methods, as well as the expected use of the results. If the purpose of testing is to find unprescribed or illicit drug use, Gas Chromatography/Mass Spectroscopy (GC/MS) and High Performance Liquid Chromatography (HPLC) are the most specific for identifying individual drugs or their metabolites.¹⁶

Caution must be exercised when interpreting UDT results in a pain practice. True negative urine results for prescribed medication may indicate a pattern of bingeing rather than drug diversion. Time of last use of the drug(s) can be helpful in interpreting UDT results.

A basic routine UDT panel should screen for the following drugs/drug classes:

Cocaine
Amphetamines/Methamphetamine (including Ecstasy)
Opiates
Methadone
Marijuana
Benzodiazepines

Urinary creatinine, pH and temperature should also be ordered and recorded to assist with results interpretation and to increase specimen reliability. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 90 °F to 100 °F.¹⁵ Urinary pH undergoes physiologic fluctuations throughout the day, but should remain within the range of 4.5 to 8.0.¹⁷ Urinary creatinine varies with state of daily water intake and hydration.¹⁷ A specimen consistent with normal human urine has a creatinine concentration greater than 20 mg/dL; less than 20 mg/dL is considered dilute and less than 5 mg/dL is not consistent with human urine.¹⁷ Test results outside of these ranges should be discussed with the patient and/or the laboratory, as necessary.

Drug class-specific windows of detection are dependent on a number of factors. The detection time of a drug in urine represents how long after administration of a drug a person continues to excrete that drug and/or metabolite at a concentration above a specific test cutoff level. Although influenced by several factors including dose, route of administration, metabolism, urine concentration and pH, the detection time of most drugs or their metabolites in urine is usually 1–3 days.^{10,16} Chronic use of a lipid-soluble drug such as marijuana may extend the window of detection to a week or more.^{16,18} Benzodiazepines and their metabolites differ widely in their elimination half-lives, which affects both their clinical effect, excretion and detection.¹⁹ The window of detection for commonly tested drugs is presented in Table 1.

The method chosen to detect a particular drug will depend on the reason for undertaking the test. Immunoassay drug tests are most commonly used. They are designed to classify substances as either present or absent and are generally highly sensitive. In pain management, specific drug identification using more sophisticated chromatographic tests is needed.

Table 1
Drug Retention Times

Drug	Retention Time
Amphetamines	48 hours
Barbiturates	Short-acting (e.g., secobarbital) 24 hours Long-acting (e.g., phenobarbital) 2–3 weeks
Benzodiazepines	3 days if therapeutic dose ingested Up to 4–6 weeks after extended use (or abuse quantities)
Cocaine metabolite (cocaine parent)	2–4 days (few hours)
Methadone	Approximately 3 days
Opiates	2–3 days (morphine/codeine) 6-acetyl morphine (metabolite of heroin) <12 hours opioids (semisynthetic/synthetic) 2–3 days ^a
Propoxyphene	6–48 hours
Cannabinoids	Light smoker (1 joint) 2–3 days Moderate smoker (4 times/week) 5 days Heavy smoker (smokes daily) 10 days Retention time for chronic smokers may be 20 days–28 days
Phencyclidine (including ketamine)	Approximately 8 days Up to 30 days in chronic users (mean value = 14 days)

Note: Interpretation of retention time must take into account variability of urine specimens, drug metabolism and half-life, patient's physical condition, fluid intake, and method and frequency of ingestion.

^aDetected by GC/MS or other high sensitivity method.

These are general guidelines only.

Combined techniques as is GC/MS make accurate identification of a specific drug and/or its metabolites possible. When the patient is being prescribed drugs from several different classes of compounds, as is the case with many pain patients, specific identification is recommended. When properly used, these tests can help reduce cost, ensure accuracy and improve efficiency.

Immunoassay is subject to cross-reactivity; i.e., substances with similar, and sometimes dissimilar, chemical composition may yield a false positive for the target drug. For this reason, specific identification of positive results (i.e., with GC/MS) is recommended. For example, immunoassay test for cocaine reacts principally with cocaine's primary metabolite, benzoylecgonine, and to a lesser extent cocaine itself.²⁰ The immunoassay test reliably identifies cocaine use. In contrast, tests for amphetamine and its derivatives are highly cross-reactive due to structural similarities to many prescription and over-the-counter (OTC) products. These include diet agents, decongestants such as ephedrine and pseudoephedrine and certain drugs used in the treatment of Parkinson's disease.

The case of amphetamine testing merits further examination. Amphetamines and their derivatives exist in two mirror image forms called isomers. While both the d- and l-isomers are biologically active, it is primarily the d-isomer that accounts for this class of drugs' central

effects and misuse potential. For example, l-methamphetamine is used in OTC medications such as Vicks[®] Nasal Inhalers (Procter & Gamble, USA). A test that is positive by immunoassay screen for methamphetamine must be confirmed by GC/MS with a level of greater than 200 ng/mL of amphetamine to be a positive test for illicit use of this drug.²¹ This situation can be avoided by the patient always informing the doctor of any OTC medication that is taken.

Tests for natural opiates are very responsive to morphine and codeine, but do not distinguish between the two. UDT by immunoassay also shows a low sensitivity for semisynthetic/synthetic opioids such as oxycodone and fentanyl.^{19,21} A negative response does not exclude their use. The synthetic opioid methadone will not be detected on a routine screening immunoassay drug panel unless specifically ordered.¹¹ The previous detection of a semisynthetic or synthetic drug does not ensure future detection, even when dose and dosing interval have not changed.

The presence of a prescribed drug in the urine sample makes monitoring of that class of drugs impossible by immunoassay technique alone. Specific drug identification by chromatographic testing (HPLC or GC/MS) is necessary to identify which member of the detected class is responsible for the positive screen. For example, a positive opiate screen cannot be explained on the basis of prescribed transdermal

fentanyl; another opioid must be responsible for the positive result.

Even though an immunoassay may be negative for consumed oxycodone, it should be positive on HPLC or GC/MS if the drug was used within the window of detection. The clinical importance of this fact with urine drug testing cannot be overstated since compliant patients may have been dismissed from pain management practices secondary to false-negative immunoassay test when looking specifically for prescribed oxycodone.

Specimen Reliability

The purpose of UDT, in the context of pain management, is to enhance patient care. Certain simple measures can be taken to improve the reliability of the results obtained from the donor's urine, including careful labeling of the sample container and the use of temperature-sensing collection bottles. An unusually hot or cold specimen, small sample volume or unusual color should raise concerns and lead to discussion with the patient. Samples collected in the early morning are usually more reliable due to increased concentration of the specimen.

Ideally, specimen collection should be done randomly. Unobserved urine collection is usually acceptable in the context of the usual pain management practice. Consult with the laboratory regarding any unexpected results.

A false-negative result is technically defined as a negative finding in a sample known to contain the drug of interest. This may occur through laboratory or clerical error or, less likely, due to tampering with the urine sample. Methods employed by a minority of patients who may attempt to influence UDT results include adulteration and substitution of urine. Adulteration and substitution should be suspected if the characteristics of the urine sample are inconsistent with normal human urine.

A less ominous reason for an unexpected negative urine drug test is that the patient has been running out of drug early due either to inadequate dosing or problematic use (i.e., bingeing). Regardless of the reason, the results must never be ignored. Schedule an appointment to discuss abnormal/unexpected results with the patient. Discuss results in a positive and supportive fashion. Use results to strength-

en the physician-patient relationship and support positive behavioral change. Always chart the results and interpretation of the UDT. There must be a clear relationship between test results and subsequent actions taken by the treating practitioner.

Caveats to Interpretation

Clinical urine drug testing, like any other medical test, must be used to improve quality of care. Inappropriate interpretation of results may adversely affect clinical decisions; for example, discharge of patients from care when prescribed drugs are not detected (compliance testing) and over- or under-diagnosis of addiction/misuse. Physicians should use UDT results in conjunction with other clinical information when deciding to continue with or adjust the established boundaries of the treatment plan.

The following examples illustrate some common urine test scenarios that may mislead the clinician.

Opiates

A patient may be unexpectedly positive for morphine due to the metabolism of prescribed codeine or in certain situations, opium alkaloids such as morphine and codeine found in foodstuffs (e.g., poppy seeds in some bread/confections).^{10,20,21} In general, codeine or morphine should not be the opioids of choice for chronic pain management in patients with a history of heroin addiction, since both heroin and codeine are metabolized to morphine.²⁰ Results of random urine drug tests, which should be part of the treatment plan, will be positive for morphine. The clinician will not know if the positive result was because of the prescribed opiate or a relapse to the use of heroin. It is only by detecting the presence of 6-monoacetylmorphine (6-MAM), a heroin metabolite, that definitive proof of heroin use is demonstrated. However, because of its short half-life of 30 minutes, this metabolite is seldom found in the urine drug test.²²

In certain cases, a UDT may detect traces of unexplained opioids secondary to drug metabolism. For example, a patient taking large quantities of codeine may show trace quantities of hydrocodone that is unrelated to hydrocodone use.²³ Detection of minor amounts of hydrocodone in urine containing a high concentration

of codeine should not be interpreted as evidence of hydrocodone misuse. In the case of a patient who is prescribed hydrocodone, quantities of hydromorphone may also be detected due to hydrocodone metabolism.¹¹

Cocaine

In general, immunoassay results for the presence of the major metabolite of cocaine, benzoylecgonine, are highly reliable. There is little that cross-reacts with this test to give a false-positive result.

In some cases, a patient may be positive for cocaine following certain medical procedures when used as a topical anesthetic. Local anesthetics, however, that end in “caine” such as lidocaine or bupivacaine do not result in a false positive for cocaine.²¹

Benzodiazepines

Benzodiazepines may pose many challenges in monitoring. Due to a variety of factors, including differences in cross-reactivity, potency and dose, the detection of benzodiazepines is highly variable.²⁴ For this reason, false-negative results are not uncommon, even in those persons using benzodiazepines as prescribed.

Unexpected Negative Urine

A negative urine test for a prescribed medication may be a result of various factors, including the patient running out of his or her medication early (bingeing). There is no reliable relationship between urine drug concentration and amount of drug ingested. It is also important to ensure that the threshold for reporting has been removed when trying to interpret the absence of any prescribed medication. Coordination between the testing laboratory and clinician will help ensure that the urine drug test results reflect accurately the clinical picture for the benefit of the patient.

In all cases, clinical judgment will play a key role in interpretation of the UDT results. The UDT complements the doctor-patient relationship by illuminating the full clinical picture in order to give patients the best quality of life given the reality of their medical conditions.

Myths About UDTs

Passive smoke inhalation rarely explains positive marijuana results when a cutoff point to declare a positive is used; therefore, a positive

UDT should be considered consistent with use of marijuana.¹⁴

Legally obtained hemp food products are increasingly available in retail stores. However, multiple studies have found that the THC concentrations typical in hemp seed products are insufficient to produce a positive immunoassay result.^{25,26}

There have been documented cases of cocaine ingestion by drinking tea made from coca leaves.²¹ Although such tea may be available for purchase by unknowing consumers, the product—containing cocaine and/or related compounds—is illegal under U.S. Drug Enforcement Administration and Food and Drug Administration regulations. Therefore, in the absence of a legitimate medical explanation, a positive cocaine test indicates illicit use.

Emerging Technologies for Drug Testing

In the past few years, several new techniques have been developed in the field of drug testing. Each has strengths and limitations that will be discussed briefly.

Saliva and sweat testing are being developed primarily for use in the forensic setting. Advantages in using saliva as a test sample include the ease of collection, minimal personal invasiveness, and limited pre-analytical manipulation. However, because drugs and/or metabolites in saliva are generally proportional to those in plasma, they are retained for a shorter period and at lower concentrations compared with urine.^{20,27,28}

Sweat collection using a sweat patch is a non-invasive, cumulative measure of drug use over a period of days to weeks, which is most appropriately used to monitor drug use in chemical dependency or probation programs.²⁹ Problems with patch adherence and sensitivity compared to UDT may limit its effectiveness.³⁰

Hair analysis provides a retrospective, long-term measure of drug use that is directly related to the length of hair tested.^{20,31} However, darkly pigmented hair appears to have a greater capacity to bind certain drugs than hair that is fair or gray, leading to the claim that hair analysis might have a racial bias.^{27,29,31} Other disadvantages of hair analysis include irregular growth (approximately half an inch per month), inability to reliably incorporate certain drugs and labor-intensive sample preparation and cost.^{27,28}

Blood testing (more correctly, serum testing) can give an accurate assessment of drug level at the blood brain barrier. While this is useful in the forensic context of assessment of impairment, blood samples are not amenable to rapid screening procedures. They also are expensive, have low drug concentrations and so relatively limited windows of detection, and require invasive collection.^{20,29} It is not recommended for routine testing.

Point of Care (POC) testing is becoming more readily available for routine use in the primary care setting. The basic principle relies on immunoassay technology to identify specific drugs or classes of drugs. It should be pointed out that these tests are designed primarily to detect drug use in a population of donors who are essentially drug free. A recent report on field evaluation of five POC test systems demonstrated a false-negative rate less than 1% for all the drugs tested (marijuana, cocaine and metabolites, amphetamine(s), opiates and PCP) and $\leq 0.25\%$ for false positives on marijuana, benzoylecgonine and opiates. PCP ($\leq 1.5\%$) and amphetamine(s) ($\leq 1.75\%$) showed the highest false-positive rates.³² In pain management, most patients are on one or more members of the drug classes being tested for. This makes POC testing of limited value in the context of pain medicine. In most cases, positive results for general classes of drugs need to be specifically identified by GC/MS in order to use UDT to its best advantage.

The cost of urine drug testing varies tremendously across the country. In this context, drug testing does not require rapid results. The ordering practitioner is encouraged to negotiate the best price for drug testing from several laboratories. As an example, one author's negotiated cost for a urine drug test using immunoassay with GC/MS identification is less than \$20.00/sample as is GC/MS without cutoff. GC/MS without cutoff is typically used to monitor compliance with patients who are prescribed semi-synthetic opioids such as oxycodone (Howard A. Heit, personal observation, 2003).

Conclusion

Urine drug testing is an effective tool for the physician in the assessment and ongoing management of patients who will be, or are being,

treated chronically with controlled substances. A working relationship with a testing laboratory may be very helpful in accurately interpreting urine test results. Most importantly, a physician should have a relationship of mutual honesty and trust with the patient when using urine drug testing in his or her clinical practice. With a carefully thought out testing strategy and accurate interpretation of the results, the interests of both the patient and practitioner are well served. The use of urine drug testing should be consensual; it is designed to improve patient care and to assist physicians to advocate on their behalf. The results should be used to enhance patient care and communication in the context of the doctor-patient relationship.

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