



# Urine Drug Testing in Clinical Practice

DISPELLING THE MYTHS  
& DESIGNING STRATEGIES

**Edition 3, 2006**



**Target Audience: Healthcare professionals who treat patients with pain.**

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## NEEDS STATEMENT

Urine drug testing in clinical practice should be a consensual diagnostic test, which is done with full explanation to and for the benefit of the patient. It can be used to provide objective documentation showing adherence to the agreed-upon treatment plan, to aid in the diagnosis and treatment of the disease of addiction or drug misuse, if present, and to advocate for the patient in family and social issues.

Questions exist regarding which test to order and how to interpret a urine drug test (UDT) result in the clinical setting. The questions include the purpose of testing, which drugs to test for, the “best” sample to test, how to collect the sample, which testing methods to use, and the level of understanding of the healthcare professionals using the resulting data. Healthcare professionals must understand the strengths and limitations of any test, including the UDT, that may alter patient management.

A healthcare professional should have a relationship of mutual honesty and trust with the patient when using the UDT in his or her clinical practice. A working relationship with your testing laboratory may be very helpful in accurately interpreting UDT results.

## LEARNING OBJECTIVES

After completing this educational activity, participants should be better able to:

1. Clarify the purpose of urine drug testing and identify a clear testing strategy.
2. Distinguish between urine drug testing for detection of illicit drug use and for monitoring adherence to a treatment regimen.
3. Describe drug-testing methodology, instrumentation, and sensitivity/specificity of results.
4. Highlight strategies to improve:
  - Analysis.
  - Interpretation of results.
5. Understand the limitations of urine drug testing.

## GOAL

The goal of this activity is to educate healthcare professionals on proper methods, uses, limitations, and evaluation of UDT results. This is in order to rationally employ testing in clinical practice to improve patient care, to protect one's practice with objective documentation of adherence to the agreed-upon treatment plan, and to advocate for patients as needed.

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## CULTURAL/LINGUISTIC COMPETENCY

New CAFP policy and California state law require that each learning activity have elements of cultural and linguistic proficiency included in the content. This activity includes these elements.

## SUPPORT GRANT

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## BACKGROUND

Drug testing has a number of purposes in clinical practice, each of which requires a clear testing strategy. Urine is generally “the best” biologic specimen for determining the presence or absence of most drugs because it has a 1- to 3-day window of detection for most drugs. In contrast, drugs and/or their metabolites would be detectable for only a matter of hours in serum. Since serum drug testing also suffers from the disadvantages of increased cost and invasive nature, urine is the preferred biologic sample.

The term urine drug “screening” is a misnomer since it implies screening for all drugs.<sup>1</sup> In reality, it is not possible to prove the presence or absence of all drugs, and the testing process is open-ended and evolving.<sup>2</sup> No “standard” urine drug test (UDT) is suitable for all purposes and settings—rather, a multitude of options exists that healthcare professionals should adapt to their clinical needs.<sup>1</sup> The healthcare professional must advise the testing laboratory whether the presence of any particular substance or group of substances is suspected or expected.<sup>2</sup> Accurately interpreting UDT results requires the healthcare professional to take a detailed history of the medications a patient uses, including over-the-counter (OTC) or herbal preparations, documentation of the time of their last use, and knowledge of which preparations, or their metabolites, may cross-react or interfere with immunoassays.<sup>3</sup>

Strong lines of communication with the laboratory personnel (eg, toxicologist, laboratory director), or technical support from the manufacturer of point-of care\* (POC) devices, are necessary to learn what can and cannot be reasonably expected of a particular test and/or laboratory.<sup>2</sup> The testing laboratory or POC device manufacturer should provide readily accessible consultation and results interpretation (eg, a manufacturer’s toll-free “hot-line”).<sup>4,5</sup> Laboratories keep specimens for a variable period of time; check with the laboratory before testing to insure a specimen is available in case additional testing is required.

Controversies exist regarding the clinical value of UDTs, partly because most current methods are designed for, or adapted from, forensic or workplace deterrent-based testing for illicit drug use.<sup>1</sup> As a result, they are not necessarily optimized for clinical applications where a number of licit prescription drugs must also be included. However, when used with an appropriate level of understanding, UDTs can improve

a healthcare professional’s ability to manage therapy with prescription drugs (including controlled substances), to diagnose substance misuse<sup>1</sup> (abuse) or addiction,<sup>4</sup> to guide treatment, and to advocate for patients.<sup>1,6-8</sup>

### Substances Detected

UDTs can detect the parent drug and/or its metabolite(s) and, therefore, demonstrate recent use of prescription medications (eg, opioids, benzodiazepines, amphetamines, barbiturates) and illegal substances (eg, heroin, illicit cocaine, marijuana, phencyclidine [PCP]).<sup>1,6,9</sup> For most clinical and forensic applications, initial testing is usually done with class-specific immunoassay drug panels, which typically do not identify individual drugs within a class. This is followed by a more specific technique to identify or confirm the presence or absence of a specific drug and/or its metabolite(s).

Many important differences exist between and within laboratories and manufactured POC UDTs; for example, the drugs included in the test menu for the immunoassay drug panels, cross-reactivity patterns, cutoff concentrations, and drug interferences.<sup>10</sup> To prevent errors in diagnosis and management, correct interpretation of test results requires knowledge and understanding of these variables.

## CURRENT USES OF URINE DRUG TESTING

### Federally Regulated Testing

Federally regulated testing is the most established use of urine drug testing. The “Federal Five” drugs or drug classes that are tested for in federal employees and federally regulated industries (eg, Department of Transportation [DOT]) are marijuana, cocaine, opiates,<sup>8</sup> PCP, and amphetamines/methamphetamines.<sup>11,12</sup>

Table 1 shows the federally mandated immunoassay screening and confirmation cutoff concentrations for the “Federal Five;”<sup>11</sup> however, the cutoff concentrations used for drugs in federally regulated testing, particularly opioids, are too high to be of value in clinical practice. Positive results based on immunoassays alone are referred to as “presumptive positives” because of factors such as cross-reactivity and different sensitivity and specificity between immunoassays.<sup>11</sup> In the federal model, the results must be confirmed by a more specific method such as gas chromatography/mass spectrometry (GC/MS).<sup>11</sup> The

\*point-of-care testing: on-site testing using commercial devices without the need for instrumentation

<sup>1</sup>substance misuse: a precise definition for substance misuse has not been established; however, a working definition is the use of any substance that harms or endangers the individual, family, or community in an individual who does not meet the criteria for addiction to that substance

<sup>4</sup>addiction: a primary, chronic, neurobiologic disease with genetic, psychosocial, & environmental factors influencing its development & manifestations

<sup>8</sup>opiate: an historical term restricted to naturally occurring alkaloids derived from opium (morphine, codeine, thebaine)

<sup>11</sup>GC/MS: gas chromatography is used to separate the different components in a specimen, & mass spectrometry is used to specifically identify the components of the specimen

**Table 1. Initial and confirmation cutoff concentrations during federally regulated testing**

Drug	Immunoassay screening cutoff concentration (ng/mL)	Confirmation cutoff concentration (ng/mL)
Marijuana metabolites THC	50 —	— 15
Cocaine metabolites Benzoylcegonine	300 —	— 150
Opiates Morphine Codeine	2000 — —	— 2000 2000
Phencyclidine	25	25
Amphetamines Amphetamine Methamphetamine	1000 — —	— 500 500

THC=11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid  
49CFR§40.29. 1994, modified 1998.

split sample\* and chain of custody<sup>†</sup> requirements for federally regulated testing are not typically applicable to clinical practice. Details of the federal program are beyond the scope of this monograph.

### Nonregulated Testing

Nonregulated testing is used for a growing range of purposes. In settings outside of the federal system, it is particularly important that the testing laboratory is aware of the purpose of testing so that they can customize their methodology and interpretation of results, if requested, to meet specific needs.<sup>1</sup>

**Forensic:** Many uses of UDTs have possible legal implications; for example, parents involved in child custody cases; applying for driver's license renewal after drug-related revocation or suspension; within the criminal justice system; for insurance, workers' compensation, or social security disability; sports testing; pre-employment screening; and random workplace testing.<sup>2,13</sup> This may require a chain of custody, provision of split samples, and secure storage of non-negative test samples, which may be requested by legal authorities after the initial testing.<sup>2,13</sup> In addition, on June 27, 2002, the US Supreme Court (Board of Education of Independent School District No. 92 of Pottawatomie County v Earls, No. 01-332) ruled that widespread random urine drug testing can be performed in public schools for all middle and high school children participating in competitive extracurricular activities.<sup>14</sup>

The scope of workplace testing often includes drugs beyond the "Federal Five;" other drugs that immunoassays are available for include methadone, propoxyphene, benzodiazepines, oxycodone, and barbiturates, with more being added continually.

**Clinical:** In contrast to forensic testing, which generally assumes that the majority of donors will be negative for substances that may have misuse liability, in therapeutic testing the vast majority of donors are in fact positive for the drug(s) of interest since these are often prescribed for legitimate medical purposes.<sup>8</sup> The initial and confirmatory testing levels for opiates in federal testing were raised from 300 ng/mL to 2,000 ng/mL in order to reduce the identification of most individuals who may be ingesting foodstuffs that contain poppy seeds.<sup>11</sup> In the clinical setting it is important that 300 ng/mL or less be used for both screening and confirmation when monitoring patients' adherence to a treatment plan. Healthcare professionals ordering the test should specify these limits to the testing laboratory and ensure that it has the capability to detect substances below the federal cutoff levels.

Urine drug testing is often used, together with an appropriate history and physical examination, to support treatment decisions made in emergency departments (eg, when the patient is reported to have misused substances, presents a variety of certain symptoms, has experienced trauma).<sup>1,15</sup> Because substance misuse or addiction are risk factors for future trauma, intervention following identification of misuse or addiction is clinically indicated for all trauma patients.<sup>1</sup>

UDTs are also used to assist in monitoring adherence to a controlled substance treatment regimen (eg, for chronic noncancer pain [CNCP]) and to assist in the diagnosis of drug misuse or addiction prior to starting or during treatment with controlled substances. Chemical-dependency programs regularly perform UDTs to monitor patients' adherence to maintenance drugs, to reinforce behavioral change, and to direct appropriate further treatment.<sup>1</sup> Other clinical uses include testing prior to medical procedures and testing pregnant women at risk for substance misuse or addiction, which may be used for treatment intervention and to assist in neonatal management.<sup>1,16</sup>

\*split sample: splitting a single urine void into two separate bottles labeled A & B; bottle A is tested; bottle B remains sealed & available for testing at the direction of the donor  
†chain of custody: a legal term that refers to the ability to guarantee the identity & integrity of the specimen from collection through to reporting of the test results

## URINE DRUG TESTING IN CLINICAL PRACTICE

The UDT can be an important tool at healthcare professionals' disposal to evaluate patients, to support assessment and diagnosis, and to advocate on behalf of patients.<sup>8</sup> Testing cannot, however, substitute for diagnostic skills or an ongoing therapeutic alliance with a patient.<sup>4</sup> Overreliance on laboratory testing without good clinical judgment can increase the focus on the test and detract from the clinical management of and clinical relationship with the patient; for example, multiple tests a week on an otherwise stable patient would generally be considered inappropriate. In addition, the clinical value of a UDT depends on the healthcare professional's interactions with the testing laboratory (or POC test manufacturer) so that he or she orders appropriate tests and understands the limits of what the UDT can and cannot detect.<sup>1,5</sup> Although most hospital laboratories do not have specific drug identification capabilities, a reference laboratory that specializes in toxicology should be able to perform both immunoassays and specific drug identification (eg, GC/MS). These capabilities will also be found in any laboratory that is certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) for federal urine drug testing. However, SAMHSA certification is limited only to the SAMHSA profile and does not cover other drug profiles and tests offered by the laboratory. When calling a laboratory, ask to speak to the director or toxicologist to determine their analytical capabilities and to clarify your testing needs, especially around reporting subthreshold positive results (eg, no limit testing).

UDTs have not often been used in clinical practice—a study that audited medical records to assess the medical management of chronic pain patients in family practices found that only 8% of physicians utilized UDTs and, when they did use them, the results were not documented in a way that indicated clinical utility.<sup>17</sup> Appropriate use of medical management techniques (eg, treatment agreements, pain scales, UDTs) may improve adherence monitoring by healthcare professionals and offer greater protection from drug misuse/addiction and diversion\*/trafficking.<sup>†</sup> This may help overcome a major barrier to effective pain relief—healthcare professionals' fear of iatrogenic addiction or relapse of previously addicted patients.<sup>17</sup>

The rationale for performing UDTs will depend on the clinical question(s) to be answered; for example, to assist in medication adherence, seeking an initial diagnosis of drug misuse or addiction, as an adjunct to

self-report of drug history, or as a requirement of continued treatment.<sup>5</sup> Frequency of testing should be determined by clinical judgment; for example, in random testing of the low-risk individual, two to three times per year may be adequate. If the patient is displaying aberrant behavior, testing frequency should be sufficient in order to document that the patient is adhering to the treatment plan and that he or she understands his or her responsibility in chronic pain management; for example, twice weekly testing during periods of obvious instability or as directed by a qualified substance abuse specialist

### WHY TO TEST

#### Patient Advocacy

With accurate record-keeping and due care, healthcare professionals can use UDTs to advocate for patients in family, workplace, and contested situations as objective documentation of adherence to the agreed-upon treatment plan.<sup>8</sup> The fact that the patient agrees to a urine drug testing program decreases the risk of an undiagnosed drug misuse problem.

#### Identify Use of Undisclosed Substances

A UDT can aid the healthcare professional to diagnose, or disprove, misuse of or addiction to illicit or non-prescribed licit drugs. UDT results that corroborate the clinical history of self-reported use should be used to assist the patient in discontinuing illicit drug use; UDT results that are in conflict with the patient's self-report should be further investigated, with significant tightening of boundaries as a condition of ongoing treatment with controlled substances (eg, limited dispensing, increased frequency of appointments, pill counts, referral to or consultation with an addiction specialist).<sup>7,8</sup> It is important to remember that drug misuse or a concurrent addictive disorder does not rule out a treatable pain problem, but requires careful evaluation and use of a treatment plan.<sup>7,8</sup> A "Universal Precautions"<sup>‡</sup> approach to the assessment and ongoing management of chronic pain patients offers a triage scheme for estimating risk and includes recommendations for management and referral (Table 2).<sup>7</sup> In addition, brief screening tools such as the Opioid Risk Tool (ORT) have a high sensitivity and specificity for determining which opioid-treated patients are at increased risk for opioid-related aberrant behavior.<sup>18</sup> The ORT can be used to trigger initial and subsequent drug testing, although a low ORT score does not rule out the need for a UDT. Other reasons for testing are to encourage healthy behavioral change by patients and to reinforce maintenance of healthy changes already made.<sup>8</sup>

\*diversion: diverting drugs from their lawful medical purpose

†trafficking: unlawful transfer of controlled drugs

‡Universal Precautions: recommendations to guide patient assessment, management, & referral to improve patient care, reduce stigma, & contain risk

**Table 2. The ten steps of Universal Precautions**

1. Make a diagnosis with appropriate differential
2. Psychologic assessment, including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Pre-/postintervention assessment of pain level & function
6. Appropriate trial of opioid therapy +/- adjunctive medication
7. Reassessment of pain score & level of function
8. Regularly assess the “Four **As**” of pain medicine\*
  - Analgesia, Activity, Adverse reactions, & Aberrant behavior
9. Periodically review pain diagnosis & comorbid conditions, including addictive disorders
10. Documentation

Gourlay DL, et al. *Pain Med.* 2005;6:107-112.

\*Passik SD, et al. *Clin Ther.* 2004;26:552-561.

### Uncovering Diversion or Trafficking

Diversion or trafficking of prescribed medications occurs when patients or others, who may or may not be drug misusers, attempt to obtain a prescription for abusable drugs for illicit distribution or sale.<sup>5</sup> When determining whether a patient is taking the medications prescribed or to decrease the risk of diversion or trafficking, it is essential to know the characteristics of the testing procedures, since many drugs are not routinely or reliably detected by all UDTs. Contact the laboratory to ensure the medication you are looking for will be reliably identified by the test ordered.<sup>19</sup> Also be aware of the ranges and reporting cutoff concentrations that a particular laboratory utilizes. The therapeutic doses of some agents might fall below the limit of detection (LOD\*) of UDTs that are designed to deter drug misuse; even misuse of substantial quantities of some drugs may not be detected. There is currently no scientifically validated relationship between the concentrations reported in the urine and the doses taken of prescribed drugs.<sup>5,20</sup>

An inappropriately negative UDT may also occur secondary to maladaptive behavior, such as bingeing, that may lead to running out early of the prescribed controlled substance.<sup>8</sup> This needs to be addressed in a therapeutic context.<sup>8</sup> Unexpected results should always be discussed with the patient and, where necessary, with the testing laboratory.

### WHOM TO TEST

Although there are no pathognomonic signs of addiction/misuse or diversion/trafficking, the clinical presentations

in the following section may be indications for closer monitoring, including increased frequency of UDTs and tightening of treatment boundaries. One recent study among chronic pain patients receiving long-term opioid therapy found that reliance on aberrant behavior alone to trigger a UDT (ie, reports of lost or stolen prescriptions, consumption in excess of the prescribed dosage, visits without appointments, multiple drug intolerances and allergies, frequent telephone calls) may miss a significant number of those individuals using unprescribed or illicit drugs.<sup>21,22</sup> Because the validity of drug users' self-reported substance use is variable, using UDTs in addition to self-report and monitoring of behavior may provide a more complete diagnostic picture.<sup>5,8,9,21-24</sup> Likewise, the appearance, ethnicity, language, or culture of a patient are not reliable indicators of aberrant drug-related behavior; performing UDTs on all patients receiving or being considered for prescription of controlled substances can help to validate and destigmatize patients.

Healthcare professionals are often presented with opportunities to initiate and support treatment for substance misuse or addiction when patients seek medical care for their complications. However, UDTs assess only the presence of a particular drug and/or its metabolite(s) in a specific concentration at a specific moment in time and do not generally provide information regarding drug addiction, physical dependence,<sup>†</sup> or impairment.

### New Patients Already Receiving a Controlled Substance

In addition to history, physical examination, contacting past healthcare professionals, and requesting past medical records, performing a UDT on a new patient who is already being treated with a controlled substance can determine whether the drug and/or its metabolite(s) are detectable in his or her urine, which would be consistent with recent use. The routine use of a UDT at the initial evaluation can increase both healthcare professional and patient acceptance of this useful test. When healthcare professionals see urine drug testing as a clinical tool rather than a pejorative test, most patients will be more comfortable with this request.

### Patients Who Are Resistant to Full Evaluation

Patients who refuse physical examination and evaluation to confirm their presenting condition, or who are reluctant to undergo diagnostic tests, including a UDT, are not candidates for therapy with a controlled substance. A UDT may still be useful in diagnosing an

\*LOD: lowest amount of drug that a laboratory can reliably identify in a specimen; the limit of detection varies depending on the methodology & laboratory

†physical dependence: a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, &/or administration of an antagonist<sup>22</sup>

underlying addictive disorder, even if the decision is made not to prescribe a controlled substance, because an untreated substance use disorder can adversely affect so many areas of a patient's life, including, mood, sleep, and function. These patients may also be unwilling to give permission to obtain past medical records or to communicate with past healthcare professionals. Never prescribe "on-demand" for a patient until you are comfortable with the situation.

### Patients Who Request a Specific Drug

Although patients may request a specific drug because it has worked for them in the past, refusal of other rational pharmacologic trials or generic substitutions is a cautionary point; for example, allergy to all but one specific drug with high misuse potential. Unwillingness to try other treatment options with no medical justification is also suspicious and merits further investigation.

### Patients Who Display Aberrant Behavior

Patients who display problematic behavior, including drug seekers, often want appointments toward the end of office hours, telephone or arrive after office hours or when their primary healthcare professional is not available, and may insist on being seen immediately because they are late (for their flight, meeting, child's soccer game, etc). Aberrant drug-related behaviors that suggest substance misuse or addiction include repeated episodes of prescription loss, resistance to changes in therapy, multiple unsanctioned dose escalations or other non-adherence to therapy despite repeated warnings, and concurrent misuse of alcohol or illicit drugs.<sup>23,25,26</sup> It is important to be aware, however, that patients who are not addicted to, misusing, or diverting drugs may display similar behaviors; for example, patients whose pain is undertreated (pseudoaddiction\*).<sup>26,27</sup> Although no aberrant behavior is pathognomonic of misuse or addiction, such behavior should never be ignored because the diagnosis of misuse or addiction is often made prospectively over time. Pseudoaddiction, however, is a diagnosis often made retrospectively; for example, previously aberrant behavior that normalized with aggressive and rational treatment of poorly controlled pain.<sup>27,28</sup>

### Patients in Recovery

Patients who have struggled with substance misuse disorders are often reluctant to accept even rational pharmacotherapy for pain management. In these cases, routine urine drug testing can provide both reassurance and objective evidence to the treatment

team, the patient, and patient's family of appropriate attention to the increased risks in this patient population. While pharmacologic treatment in these patients is never without risk, risk can and should be managed.

## WHEN TO TEST

### When Considering Treatment With a Controlled Substance

Although only a minority of patients either misuse or become addicted to their prescribed medications, those who do generally have a current or past history of substance misuse or addiction.<sup>19</sup> There is no evidence in the literature that rational pharmacotherapy for the treatment of any medical condition leads to iatrogenic addiction; however, there is little evidence to the contrary either. Therefore, routine screening for a history of misuse or addiction in all patients is appropriate before prescribing any medication, especially a controlled substance.<sup>19</sup> This may include a UDT to determine whether the patient is taking or has recently taken illicit and/or licit nonprescribed substances.<sup>19</sup>

A history of substance misuse does not preclude appropriate treatment with any medication, including a controlled substance, when indicated (eg, opioid<sup>†</sup> analgesia to relieve pain), but does require a treatment plan with firmly defined boundaries.<sup>7</sup> Clinically, a patient in recovery from the disease of addiction can be safely managed by setting careful and strict boundaries, which include random UDTs, a treatment agreement, and referral to, or comanagement with, a recovery program<sup>‡</sup> or expert in the management of such patients.<sup>29</sup> A patient with active addictive disease must start a program for recovery to increase the success of the treatment of their pain syndrome.<sup>8</sup> Chronic pain problems cannot be solved in the face of active, untreated addiction.

The US Code of Federal Regulations for prescribing a Schedule II controlled substance clearly states that a controlled substance can be prescribed for the treatment of pain in any patient, including those with a history of substance misuse or addiction.<sup>30</sup> A summary of federal regulations for prescribing a controlled substance can be found on the American Society of Addiction Medicine Web site ([http://asam.org/pain/federal\\_regulations\\_for\\_prescrib.htm](http://asam.org/pain/federal_regulations_for_prescrib.htm)).<sup>31</sup> It must be emphasized that the controlled substance is prescribed to treat the pain syndrome, not for maintenance or detoxification of a concurrent addictive disorder. The records must reflect a clear evaluation of the presenting complaint,

\*pseudoaddiction: an iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain management

<sup>†</sup>opioid: a more current term that includes opiates & synthetic/semisynthetic agents that exert their effects by binding to highly selective opioid receptors

<sup>‡</sup>recovery program: an ongoing process to help the patient develop coping strategies & tools for abstaining from drug use & then maintain abstinence

the treatment plan, appropriate follow-up of the pain syndrome, and a clear indication for the medical use of opioid therapy. The terms “taper” or “wean” and “detoxification” must not be used interchangeably— from a regulatory standpoint, opioid detoxification using methadone is a practice reserved for those healthcare professionals who are registered as a Narcotic Treatment Program with the Drug Enforcement Administration (DEA) or who have received a waiver from the Center for Substance Abuse Treatment of the SAMHSA under the Drug Addiction Treatment Act of 2000 for office-based opioid treatment using buprenorphine with or without naloxone.

### When Making Major Changes in Treatment

Modification of therapy, particularly dose increase, should depend on the evaluation of progress toward stated treatment objectives, which are decreased pain and increased function, while monitoring for side effects. If treatment objectives are not being achieved despite medication adjustments, a UDT may assist with monitoring patient adherence before making further changes to the treatment plan. If concerns arise that a patient is misusing the prescribed medication or other substances, UDT results may be helpful for documentation and to guide treatment.

### Support Decision to Refer

The Federation of State Medical Boards’ Model Policy for the Use of Controlled Substances for the Treatment of Pain recommends that special attention, such as monitoring, documentation, and consultation/referral, should be given to patients who are at risk for misusing medications (eg, history of substance misuse or addiction, comorbid psychiatric disorder).<sup>29</sup>

Unexpected positive or negative UDT results are useful to suggest and support a decision to refer a patient to a specialist experienced in treating patients with complex conditions, such as a pain management specialist who is knowledgeable in addiction medicine.<sup>19,29</sup>

### Treatment Agreements

A clearly understood and well-defined description of treatment boundaries (eg, pill counts, a urine specimen for testing when requested) should be in place when treating any patient with a chronic illness, including CNCP. The written or oral agreement should outline both the patient’s and the healthcare professional’s rights and responsibilities.<sup>29,32,33</sup>

## URINE DRUG TESTING METHODS

There are typically two types of urine drug testing. These approaches used in proper combination can reduce cost, ensure accuracy, and improve efficiency. Although a range of technologies is available, from single-use devices to fully automated laboratory platforms, the two main types of UDT are:

1. Immunoassay drug testing, either laboratory based or at POC (eg, “dip-stick” testing).
2. Laboratory-based specific drug identification (eg, GC/MS, high-performance liquid chromatography [HPLC]).

The method chosen to detect a particular drug will depend on the reason for undertaking the test. The immunoassay drug tests are the most common methods, which are designed to classify substances as either present or absent according to a predetermined cutoff threshold. In some cases, specific drug identification using more sophisticated tests is needed, such as GC/MS. Such combined techniques permit accurate identification of a specific drug and/or its metabolite(s).

### IMMUNOASSAYS

Immunoassays, which are based on the principle of competitive binding, use antibodies to detect the presence of a particular drug or metabolite in a urine sample.<sup>11</sup> A known amount of an antibody and the drug or metabolite that has been labeled with an enzyme are added to the urine sample. The drug or metabolite in the sample will compete with the labeled drug or metabolite to bind antibody to form antigen-antibody complexes. The amount of enzyme-labeled antigen that binds with antibody is inversely proportional to the amount of drug and/or its metabolite(s) in the sample.

The principal advantage of immunoassays is their ability to simultaneously and rapidly test for drugs in urine. Their principal disadvantage is that they vary in the range of compounds detected, some detecting specific drugs while others recognize only classes of drugs. An immunoassay’s ability to detect drugs will vary according to the drug concentration in the urine and the assay’s cutoff\* concentration. Any response above the cutoff is deemed positive, and any response below the cutoff is negative (eg, if the cutoff is set at 50 ng/mL, 49 ng/mL will be reported as negative). Immunoassays are also subject to cross-reactivity;<sup>11</sup> ie, substances with similar, and sometimes dissimilar, chemical composition may cause a test to appear

\*cutoff: the drug concentration above which an assay reports a positive result & below which the result is negative

positive for the target drug. For example:

- Tests for cocaine react principally with cocaine and its primary metabolite, benzoylecgonine. These tests have low cross-reactivity with other substances and, therefore, are highly predictive of cocaine use.
- Tests for amphetamine/methamphetamine are highly cross-reactive. They may detect other sympathomimetic amines such as ephedrine and pseudoephedrine and, therefore, are less reliable for amphetamine/methamphetamine use. Further testing may be required by a more specific method, such as GC/MS and stereospecific chromatography (see page 13 for more details). Consultation with an individual knowledgeable in UDT interpretation (eg, laboratory director or toxicologist) is strongly encouraged, especially when unexpected test results are obtained.
- Standard tests for opiates are very responsive for morphine and codeine, but do not distinguish which is present. They also show a lower sensitivity for semisynthetic/synthetic opioids such as oxycodone, oxymorphone, buprenorphine, (which is now becoming clinically used in maintenance therapy for opioid addiction, as well as off-label for pain management),<sup>34</sup> fentanyl, and methadone (which is used for the treatment of pain [if the healthcare professional has a license to prescribe a Schedule II controlled substance] or to treat addiction [provided the healthcare professional is registered as a Narcotic Treatment Program with the DEA]);<sup>30</sup> a negative result does not exclude use of these opioids. Specific immunoassay tests for some semisynthetic/synthetic opioids may be available.

Therefore, for clinical purposes, the cocaine assay would be very reliable, while the amphetamine assay would be unreliable in predicting use of the drug. Samples that test positive by immunoassay for classes of drug should be tested in the laboratory by an alternative method to identify specific drugs. It is important to discuss the testing methodology with the laboratory to determine which drugs are detected and which are not. A sample that tests positive for opiates may not include the prescribed drug, while a negative opiate test may not exclude the drug of interest. When specifically looking for the presence of a prescribed medication, it is advisable to notify your laboratory in advance to determine if more sensitive testing should be included.

### POINT-OF-CARE TESTING

A number of single-use immunoassay devices, without the need for instrumentation, are commercially available for POC testing of common classes of misused drugs.<sup>10</sup> POC UDTs typically use immunochromatographic methods that produce visually read results.<sup>10</sup> However, POC testing by immunoassay in isolation is often inadequate in clinical practice because one wants to identify the presence of a specific drug or metabolite, not the drug class. Most POC tests are based on competitive binding to antibodies by drug(s) present in the urine and a drug conjugate that is bound to a porous membrane.<sup>10</sup> In the absence of the drug in the sample, a limited number of dye-conjugated antibodies bind the immobilized drug conjugate, forming a colored line (negative result) in the test window.<sup>10</sup> When the amount of drug in a urine sample is equal to or exceeds the cutoff concentration of a particular device, the drug saturates the antibody, preventing antibody from binding the immobilized drug conjugate, so no line forms in the window (positive result)—this is a counterintuitive response. However, some POC devices now operate more logically and produce a color for a positive result. Be sure to review the testing instructions before using POC tests.

POC devices have a rapid turn-around-time, are portable, and are easy to use, requiring little training to achieve proficiency.<sup>10</sup> Potential disadvantages of these tests include the subjective nature of the qualitative assays, lack of adequate quality assurance and quality control (eg, the integrity of the test reagents following transportation and storage), data management issues, and cost.<sup>10,35</sup> In contrast to testing laboratories, POC devices purchased from a manufacturer do not include independent scientific support (eg, from a laboratory director). Therefore, the healthcare professional should carefully evaluate a POC device before routine use and use such devices with caution to prevent misinterpretation of the results generated. Most manufacturers have a toll-free “hot-line” for consultation.

### LABORATORY-BASED SPECIFIC DRUG IDENTIFICATION

Laboratory-based specific drug identification is needed in two instances: first, to specifically confirm the presence of a given drug; for example, that morphine is the opiate causing the positive immunoassay response; and second, to identify drugs not included in a screening test. For example, the semisynthetic

**Table 3. Detection time of drugs of misuse in urine**

Drug	Cutoff level (ng/mL)	Detection time in urine*
Amphetamine (multidrug misusers, dose unknown)	1000	Up to 5 days
THCCOOH after smoking 1 marijuana cigarette	50	2 to 4 days <sup>†</sup>
Benzoyllecgonine after 20 mg IV cocaine	300	Up to 1.5 days
Benzoyllecgonine after street doses of cocaine <sup>‡</sup>	300	2 to 3 days; up to 1 week at higher doses
Morphine from low-dose heroin (3-12 mg) <sup>‡</sup>	300	1 to 1.5 days

THCCOOH=9-carboxy- $\Delta^9$  tetrahydrocannabinol; IV=intravenous

\*May not accurately reflect detection after extraordinarily high doses in chronic users; <sup>†</sup>Administered via different routes; <sup>‡</sup>Up to 1 month with frequent use

Adapted from Vandevenne M, et al. *Acta Clinica Belgica*. 2000;55:323-333.

opioids hydromorphone and hydrocodone are not included, and therefore are not reported, in the federal program, although they may be detectable. The semisynthetic opioids oxycodone and oxymorphone will not typically be detected even at the 300 ng/mL cutoff. A positive immunoassay opiate screen in the context of these prescribed opioids necessitates more specific identification of the substance(s) that account for the positive result. Generally, more definitive procedures are required (eg, HPLC, GC/MS). The synthetic opioids fentanyl and meperidine will not be detected by current opiate immunoassays.

#### DRUG-CLASS–SPECIFIC WINDOWS OF DETECTION

The detection time of a drug in urine indicates how long after administration a person excretes the drug and/or its metabolite(s) at a concentration above a specific test cutoff concentration.<sup>36</sup> Although it is governed by several factors, including dose, route of administration, metabolism, urine volume, and pH, the detection time of most drugs in urine is 1 to 3 days (Table 3).<sup>4,36</sup> Long-term use of lipid-soluble drugs such as marijuana, diazepam, or PCP may extend the window of detection to a week or more.

#### IMPROVING RELIABILITY OF TESTING

##### Specimen Collection

The purpose of a UDT in the clinical context, where the vast majority of patients are not going to tamper with their urine sample, is to enhance patient care. However, certain measures can be taken to improve the reliability of the results obtained, including careful labeling of the sample container. An unusually hot or cold specimen, small sample volume, or unusual color should raise concerns.

#### Characteristics of Urine

The characterization of a urine specimen\* is based on its appearance, temperature, pH, urinary creatinine concentration, and specific gravity.<sup>11,37</sup> The color of a urine specimen is related to the concentration of its constituents. Concentrated urine samples are more reliable than dilute samples. A urine specimen may be colored because of endogenous/exogenous substances derived from food pigments, medications, or disease states that produce excessive analytes.<sup>†</sup> Urine can appear colorless as a result of excess hydration due to diet, medical condition, or water intake. In the absence of underlying renal pathology, patients who repeatedly provide dilute urine samples should be advised to decrease water intake prior to testing and to provide samples in the early morning when urine is likely to be most concentrated.

The temperature of a urine sample within 4 minutes of voiding should fall within the range of 90°F to 100°F.<sup>37</sup> Urinary pH undergoes physiologic fluctuations throughout the day, but should remain within the range of 4.5 to 8.0.<sup>37</sup> Urinary creatinine varies with state of daily water intake and hydration.<sup>37,38</sup> A specimen consistent with normal human urine has a creatinine concentration greater than 20 mg/dL; less than 20 mg/dL is considered dilute,<sup>‡</sup> and less than 5 mg/dL is not consistent with human urine. Test results outside of these ranges should be discussed with the patient and/or the laboratory, as necessary.

\*Ideally, the specimen should be 30 mL or greater to ensure reliability

<sup>†</sup>analyte: any material or chemical substance subjected to analysis

<sup>‡</sup>dilute: a urine specimen that has a creatinine concentration <20 mg/dL

**PRACTICAL STRATEGIES**

- Select a testing laboratory or POC device supplier.
- Establish a routine UDT immunoassay panel.
  - Recommended drugs/drug classes to screen for are:
    - Cocaine
    - Amphetamines (including ecstasy)
    - Opiates
    - Methadone
    - Marijuana
    - Benzodiazepines.
  - Additional tests may be added as needed.
- Drug identification:
  - GC/MS, or other chromatographic technique, identification for all patients prescribed opioids.
    - Specify “no threshold” testing at the LOD to increase likelihood of detecting prescribed medications.
  - Many laboratories have a specific chromatographic pain panel that may include one or more of the following:
    - Codeine
    - Morphine
    - Hydrocodone
    - Hydromorphone
    - Oxycodone
    - Fentanyl
    - Buprenorphine.
- Specimen collection:
  - Random collection is preferred.
  - Unobserved urine collection is usually acceptable.
  - If tampering is suspected, check urine temperature, pH, and creatinine concentration, and consider ordering an “adulteration panel”<sup>\*</sup> from your laboratory.
- UDT results:
  - Consult with laboratory regarding ANY unexpected results.
  - Schedule an appointment to discuss abnormal/unexpected results with the patient; discuss in a positive, supportive fashion to enhance readiness to change/motivational enhancement therapy (MET) opportunities.
  - Use results to strengthen the healthcare professional-patient relationship and to support positive behavior change.
  - Chart results and interpretation.

**INTERPRETATION OF UDT RESULTS**

Urine drug testing in clinical practice, like any other medical test, should be performed to improve patient care. Inappropriate interpretation of results, as with any other diagnostic test, may adversely affect patient care; for example, discharge of patients from care when prescribed drugs are not detected (adherence testing<sup>\*</sup>) and over- or under-diagnosis of substance misuse or addiction. Healthcare professionals should use UDT results in conjunction with other clinical information and consult with the laboratory or POC test manufacturer as indicated.

**SENSITIVITY AND SPECIFICITY**

The qualitative immunoassay drug panel reports each sample as either positive or negative for a particular drug or drug class, based on predetermined cutoff concentrations. In the ideal world, a UDT would be positive if the patient took the drug (true positive) and negative if the drug was not taken (true negative) (Table 4). However, false-positive or -negative results can occur, so it is imperative to interpret the UDT results carefully.<sup>3</sup> In addition, testing technology is constantly evolving and varies by manufacturer, so false-positive or -negative results today may not be relevant in the future.

In this context, the sensitivity of a test is the ability to detect a class of drugs, while the specificity is the ability to identify a particular drug. A highly specific test gives few false-positive results and identifies individual drugs and/or their metabolites. High sensitivity is due, in part, to the test’s ability to detect both the parent drug and/or its metabolite(s), combined, to reach the cutoff concentration for a positive report.

**CROSS-REACTIVITY**

Detection of a particular drug by a drug-class-specific immunoassay depends on the structural similarity of that drug or its metabolite(s) to the compound used for standardization, and the urine concentration of that drug/metabolite, compared with the standardizing

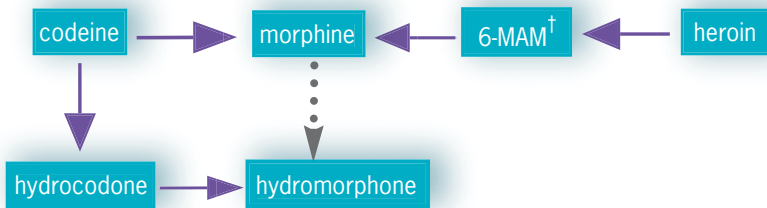
**Table 4. Interpretation of urine drug test results**

	Patient has taken drug	Patient has not taken drug
Positive test result	True positive	False positive
Negative test result	False negative	True negative

Wolff K, et al. *Addiction*. 1999;94:1279-1298.

<sup>\*</sup>adulteration panel: method to determine the characteristics of urine (eg, specific gravity, creatinine level) & to check for the presence of common adulterants. Most laboratories that do routine drug testing are familiar with tests for adulteration

<sup>†</sup>adherence testing: assessment of a patient’s adherence to a treatment plan

**Figure 1. Metabolism of opioids\***

\*Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs  
 †6-MAM=6-monoacetylmorphine, an intermediate metabolite

compound.<sup>10</sup> For example, the ability of opiate immunoassays to detect certain opioids, such as oxycodone or oxymorphone, varies among assays because of differing cross-reactivity patterns.<sup>10</sup> Methadone, a synthetic opioid, does not trigger a positive “opiate” immunoassay result; a specific methadone test is needed. In the cases of oxycodone, oxymorphone, buprenorphine, and fentanyl, even large concentrations in the urine may not be reliably detected.<sup>39</sup> Fortunately, GC/MS assays on the same urine specimen will normally detect these semisynthetic and synthetic opioids, especially if cutoff concentrations are lowered to the LOD—a so-called “no cutoff” request.

Cross-reacting compounds can also be structurally unrelated to the standardizing compound. For example, several quinolone antibiotics (eg, levofloxacin, ofloxacin) can potentially cause false-positive results for opiates by some common immunoassays, despite no obvious structural similarity with morphine.<sup>40,41</sup> Quinolones are not misidentified as opiates by GC/MS. There have also been cases of false-positive fentanyl results with some immunoassays for patients who are taking the antidepressant trazodone,<sup>42</sup> and the antidepressant venlafaxine can cause false-positive PCP results with some immunoassays.<sup>43,44</sup>

### TRUE-POSITIVE RESULTS

Positive UDT results reflect recent use of the drug because most substances in urine have detection times of only 1 to 3 days.<sup>4</sup> Long-term use of lipid-soluble drugs, such as marijuana, diazepam, or PCP, are exceptions—body fat may contain enough drug or drug metabolites to test positive for a week or more. Positive results do not usually provide enough information to determine the exposure time, dose, or frequency of use.<sup>4</sup>

### True-Positive Results That Are Misleading

**Opiates:** For patients not prescribed morphine, the presence of morphine in urine is often assumed to be

indicative of heroin use.<sup>5</sup> However, a morphine-positive UDT may also result from codeine and from morphine in foodstuffs (eg, poppy seeds\* in some breads/confectionery).<sup>3,5,11,45</sup> A specimen that tests positive for morphine with the presence of 6-monoacetylmorphine (6-MAM), a heroin metabolite, is definitive proof of recent heroin use (Figure 1).<sup>11</sup> The window of detection for 6-MAM is only a few hours after heroin use due to its short biologic

half-life in the body of 25 to 30 minutes. Heroin has an even shorter biologic half-life of 3 to 5 minutes and is seldom detected in a UDT.<sup>11,36,46</sup> When heroin use is suspected or reasonable to consider in your area, ask your laboratory under what conditions would they test for 6-MAM. Since 6-MAM spontaneously degrades to morphine, suspected 6-MAM positive specimens should be frozen to preserve them for retesting, if necessary.

### True-Positive Results With a Medical Explanation

In certain cases, a patient may have a positive UDT because of medication prescribed by another healthcare professional, use of OTC products, or consumption of certain foodstuffs that result in a positive screen.<sup>11</sup> Healthcare professionals should maintain a list of all prescription and OTC products that a patient is taking while being prescribed controlled substances, and require patients to notify them prior to adding any new medication. Documenting these agents prior to performing a UDT will assist in interpreting both true-positive and false-positive results.

**Opioids:** (Figure 1)

- Codeine is metabolized to morphine, so both substances may occur in urine following codeine use:<sup>3,5,11</sup>
  - A prescription for codeine may explain the presence of both drugs in the urine.
  - A prescription for codeine does not normally explain the presence of only morphine.† This is most consistent with use of morphine or heroin.
  - Prescribed morphine cannot account for the presence of codeine.
    - Codeine metabolizes to morphine, but the reverse does not occur.
  - Codeine alone is possible because a small proportion of patients lack the cytochrome

\*The following rule out poppy seed ingestion alone: codeine >300 mg/mL without morphine (consistent with codeine use); a morphine/codeine ratio <2 (consistent with codeine use); and morphine >1,000 ng/mL without codeine (consistent with morphine use)

†Because of codeine metabolism, samples collected 2 to 3 days after codeine ingestion may appear to contain only morphine

P450 2D6 enzyme necessary to convert codeine to morphine.

- Clinical experience of the authors suggests that morphine may be metabolized to produce small amounts (generally < 10%) of hydromorphone, possibly through keto-enol tautomerization.<sup>47</sup>
- Metabolism of codeine may produce small quantities of hydrocodone.<sup>48</sup>
- Hydrocodone may be metabolized to small quantities of hydromorphone.<sup>49,50</sup>

**Cocaine:** Cocaine is a topical anesthetic clinically used in certain trauma, dental, ophthalmoscopic, and otolaryngologic procedures.<sup>11</sup> A patient's urine may test positive for the cocaine metabolite, benzoylecgonine, after such a procedure for up to 2 to 3 days. However, a licensed healthcare professional must order its use, which can be checked through medical records or by contacting the treating healthcare professional. There is no structural similarity between other topical anesthetics that end in "caine" (eg, procaine, lidocaine) and cocaine or benzoylecgonine; therefore, cross-reaction does not occur. A positive UDT result for the cocaine metabolite, in the absence of a medical explanation, should be interpreted as due to deliberate use.

**Amphetamine/Methamphetamine:** Clinical interpretation of positive amphetamine and methamphetamine results can be challenging because of the structural similarities of many prescription and OTC products, including diet agents, decongestants, and selegiline used in the treatment of Parkinson's disease. Knowledge of potential sources of amphetamine and methamphetamine can prevent misinterpretation of results.

The traditional GC/MS criteria for reporting a positive methamphetamine result (concentration of methamphetamine > 500 ng/mL with a concentration of amphetamine  $\geq$  200 mg/mL) is not sufficient to distinguish methamphetamine use from OTC products. Methamphetamine exists as two isomers that are designated *d*- and *l*-.<sup>11</sup> The *d*-form has a strong stimulant effect on the central nervous system (CNS) and high misuse potential, while the *l*-form in therapeutic doses has a primarily peripheral action and is found in some OTC preparations. Routine testing, such as immunoassays or GC/MS, does not differentiate between the *d*- and *l*-forms, but specialized tests, such as stereospecific chromatography, can distinguish between the two

forms. Therefore, if a healthcare professional suspects amphetamine or methamphetamine misuse, stereospecific chromatography may need to be used in addition to GC/MS.

For example, the OTC Vicks® Inhaler marketed in the United States contains *l*-desoxyephedrine—the *l*-form of methamphetamine.<sup>11</sup> Patients whose management includes urine drug testing should be advised not to use the Vicks® Inhaler or similar OTC preparations containing this agent because they can interfere with the interpretation of UDT results; this is particularly important in a community with a high incidence of methamphetamine misuse. Misuse of even the *l*-form can have significant CNS activity and should be addressed clinically with the patient. The Vicks® Inhaler distributed in Canada does not contain desoxyephedrine.

#### FALSE-POSITIVE RESULTS

False-positive results can be reported because of technician or clerical error.<sup>3</sup> These results may also occur because of cross-reactivity with other compounds found in the urine. GC/MS and similar technologies are not influenced by cross-reacting compounds.<sup>4,11,40</sup> Review all positive results with the patient to explore possible explanations. All unexpected results should be verified with the laboratory to ensure their accuracy.

#### TRUE-NEGATIVE RESULTS

In most cases, negative UDT results are considered a good thing. In adherence testing, however, we look for and expect to find prescribed medications or their metabolites in the urine. UDT results positive for prescribed medications and negative for undisclosed licit and illicit drugs should be reassuring to both the patient and healthcare professional. The fact that the patient and healthcare professional have agreed to these tests can suggest a positive therapeutic alliance. The ability to advocate on behalf of patients is increased with objective evidence of adherence to the treatment program. Any unexpected positive result for drugs of misuse may indicate a substance-related problem that might otherwise have been missed. The positive result must not be ignored and may indicate a need for closer monitoring and/or possible referral to a specialist in substance misuse.<sup>7</sup> Although it does not diminish the patient's complaint of pain, it does complicate the management of it.

A true-negative immunoassay result may only mean that at the time of specimen collection, concentrations

of those substances for which the test was performed were below the threshold limits required to report a positive result.<sup>3,4</sup> This may be the result of diverting the prescribed medication or running out of the drug early because of “bingeing.” In the context of adherence testing, this can adversely affect the therapeutic alliance; therefore, consultation with the patient and/or testing laboratory is indicated. Additional, specific testing of the specimen may be necessary.

Healthcare professionals should be aware of the time taken for drugs to be eliminated from the body since it is possible that a negative test could result from not sampling soon enough after drug consumption. Time of last use and quantity of drug(s) taken can be helpful in interpreting UDT results.

### FALSE-NEGATIVE RESULTS

A false-negative result is technically defined as a negative finding in a sample known to contain the drug of interest.<sup>5</sup> This may occur through laboratory or clerical error or, less likely, through 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. Urine creatinine measurement is one method to test specimen validity; it is inexpensive to perform, easily automated, and well characterized.<sup>11</sup> The pH and other tests, such as an adulteration panel, are also useful.<sup>11</sup>

### CAVEATS TO INTERPRETATION

#### Drug Metabolites

In certain cases, a UDT may detect traces of unexplained opioids. For example, a patient who is prescribed codeine may show trace quantities of hydrocodone that may not represent hydrocodone use.<sup>48</sup> 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 be detected because of hydrocodone metabolism (Figure 1).<sup>49,50</sup> A minor metabolite should not be in excess of its parent—this is consistent with the use of the second drug. As with any unexplained test result, it is important to clarify the interpretation with someone knowledgeable in clinical toxicology.

#### Illicit/Unprescribed Drug Use

Urine drug testing can be a very effective means of identifying inappropriate drug use in clinical practice. Careful interpretation of the results will ensure their accuracy. A UDT result reported as “not detected” may not necessarily mean the patient has not used the drug, but may mean any of the following:

- The patient has not recently used drugs.
- The patient excretes drugs and/or their metabolites at a different rate than normal (eg, rapid metabolism, pH effects of the urine).
- The test used was not sufficiently sensitive to detect the drugs at the concentration present.
- Clerical/technical errors caused a positive UDT to be reported as negative.

#### Pitfalls of Monitoring Prescribed Medications

**Adherence Testing:** In the case of adherence testing, we are looking for the presence of a prescribed medication or medications as evidence of their use. In this setting, not finding a drug (true negative) is a concern and certainly merits further investigation with the patient and the testing laboratory. One or a combination of the following may lead to not finding a prescribed medication in the patient’s urine:

- The patient did not use the medications.
- The patient has not recently used the medications.
- The patient excretes medications and/or their metabolites at a different rate than normal (eg, rapid metabolism, pH effects of urine).
- The test used was not sufficiently sensitive to detect the medications at the concentration present.
- Clerical errors caused a positive UDT to be reported as negative.

In this case, a false-negative result may lead to concerns about misuse (ie, escalating dose leading to running out, bingeing, or worse, diversion). The most appropriate use of a negative result for a prescribed medication is to initiate a dialog with the patient to clarify this result.

**Synthetic/Semisynthetic Opioids:** The most widely used opiate immunoassay detects morphine and codeine, but does not reliably detect semisynthetic opioids, such as oxycodone, oxymorphone, buprenorphine, or hydromorphone (Table 5). It is possible that some semisynthetic opioids, even at high concentrations, will be inconsistently detected by the immunoassay because of incomplete cross-reactivity.<sup>11</sup>

**Table 5. Source of opioid analgesics**

Natural (from opium)	Semisynthetic (derived from opium)	Synthetic (man-made)
<ul style="list-style-type: none"> <li>▪ codeine</li> <li>▪ morphine</li> <li>▪ thebaine</li> </ul>	<ul style="list-style-type: none"> <li>▪ hydrocodone</li> <li>▪ oxycodone</li> <li>▪ hydromorphone</li> <li>▪ oxymorphone</li> <li>▪ buprenorphine</li> </ul>	<ul style="list-style-type: none"> <li>▪ meperidine</li> <li>▪ fentanyl series</li> <li>▪ propoxyphene</li> <li>▪ methadone</li> </ul>

Current opiate immunoassays do not detect synthetic opioids, such as methadone. However, GC/MS can reliably identify most opioids when present.<sup>11</sup> If the purpose behind the test is to document the presence of a prescribed medication such as oxycodone (adherence testing), the laboratory should be informed of this. It is recommended that the laboratory be instructed to remove the cutoff concentration (reporting threshold) so the presence of lower concentrations of the prescribed drug can be documented. This will greatly reduce the risk of missing a drug that is, in fact, present. In a recent study of physician practices and knowledge, however, only 12% of primary care physicians correctly knew that testing for oxycodone must be specifically requested when ordering a UDT.<sup>51</sup> Most respondents were unaware that oxycodone is not detected by most opiate immunoassays.

**Benzodiazepines:** Variability in immunoassay cross-reactivity also applies to benzodiazepines. While many benzodiazepines are generally detected by immunoassay, certain benzodiazepines, such as clonazepam, are not detected by all immunoassays. Depending on the assay used, the presence of a positive immunoassay test result in the context of a clonazepam-maintained patient should lead the healthcare professional to contact the laboratory and perform a confirmatory test. If necessary, look for an alternative source of benzodiazepine, including relapse to misuse of or addiction to the previous benzodiazepine.

**Concentration Effects:** It is important to know the threshold concentrations that your laboratory uses when interpreting a report of “no drug present.”<sup>1,3</sup> A drug may be present in the sample, but below the laboratory’s cutoff concentrations. Measuring creatinine in the urine sample will indicate if the urine is dilute, which may affect the detection of substances that are around the threshold concentration for reporting (eg, prescribed medications at therapeutic levels).

Positive results in dilute urine are readily interpretable, but a negative result in dilute urine can be problematic. Ask for “no threshold” testing to determine if the drug is present at low concentrations; however, all methods have some analytical point (the LOD) below which measurements are unreliable.<sup>1</sup>

**Amount of Drug Taken:** At this time, there is no scientifically validated relationship between the amount of drug taken and urine drug concentration. Therefore, a UDT cannot indicate the amount of drug taken, when the last dose was administered, or the source of that drug.<sup>1-5</sup> Recently, some laboratories have offered technology to compare a patient’s UDT result to an expected range for a drug—they claim that comparing a normalized test result concentration to the expected range can measure compliance with the prescribed dose (reporting: in range, low, or high). Although their protocol may calculate a normalized value based on the patient’s height and weight, the specimen’s pH and specific gravity, and prescription dosage, many other factors can influence the absorption, distribution, metabolism, and elimination of a drug. These include genetic polymorphisms (eg, enzyme deficiencies), renal and hepatic function, disease states, body surface area and muscle mass, cardiac output, drug-drug interactions, drug-food interactions, and age. Therefore, at this time, UDT measurements should not be used to extrapolate backward and make specific determinations regarding dose and compliance with the prescribed drug. Software and laboratory products have not yet been fully validated scientifically and peer reviewed in the medical literature. Interpreting a UDT beyond the current scientific knowledge may put healthcare professionals and patients at medical and/or legal risk.

## MYTHS

### Passive Inhalation

Passive smoke inhalation does not explain positive marijuana results at typical cutoffs (50 ng/mL).<sup>4,11</sup> If a positive result occurs, counseling the patient about the use of marijuana and reinforcing the boundaries set out in the treatment agreement will be more useful than taking a confrontational approach. Repeated positive results for marijuana should be viewed as evidence of ongoing substance misuse that requires further evaluation and possible treatment.

### Medical Cannabinoids

The main active ingredient of marijuana (*Cannabis sativa L.*) is 11-nor-delta-9-tetrahydrocannabinol-9 (THC).

THC has been prepared synthetically and marketed under the trade name Marinol® for the control of nausea and vomiting in cancer patients receiving chemotherapy and as an appetite stimulant for AIDS patients.<sup>52</sup> The synthetic cannabinoid called nabilone (Cesamet®) is marketed in Canada for the same indications, and is in the pipeline in the United States.<sup>53</sup> Another drug currently available in Canada is Sativex® containing THC and cannabidiol extracted from *Cannabis sativa L.*, which is indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

Smoked cannabis, orally administered Marinol®, and buccal Sativex® all produce immunoassay-positive screen results for the THC metabolite 11-nor- $\Delta^9$ -tetrahydrocannabinol-9-carboxylic acid (THCA). More specific testing may be able to distinguish between natural and synthetic THC. However, Cesamet® does not trigger a positive immunoassay screen or a confirmatory GC/MS for THCA because it does not contain THC.<sup>53</sup> There have been reports of false-positive urine immunoassay tests for cannabinoids in patients receiving proton pump inhibitors, such as pantoprazole (Protonix®).<sup>54</sup> However, a confirmatory test such as GC/MS will not verify the positive immunoassay result.

### Hemp Products and Coca Tea

Legally obtained hemp food products are increasingly available in retail stores. Although hemp products do not appear to be psychoactive, there have been concerns that ingestion of these food products, which contain traces of THC, may cause a positive UDT result for cannabinoids.<sup>55,56</sup> However, multiple studies have found that the THC concentrations typical in hemp products are sufficiently low to prevent a positive immunoassay result.<sup>55,56</sup>

There have been documented cases of cocaine ingestion by drinking tea made from coca leaves.<sup>11</sup> Although such tea may be available for purchase by unknowing consumers, the product—containing cocaine and/or related metabolites—is illegal under the US DEA and the Food and Drug Administration regulations. Patients should be advised not to ingest hemp products or coca tea.

## EMERGING TECHNOLOGIES FOR DRUG TESTING

Factors that influence the selection of a biologic specimen for drug analysis include ease of collection, analytical and testing considerations, and interpretation of results.<sup>3,5,57</sup> Urine is currently the most widely used and extensively validated biologic specimen for drug testing. Although alternative technologies using other biologic specimens are marketed for drug testing, information is lacking about false-positive and -negative results, interferences, and cross-reactivity. The relative detection times of drugs in biologic specimens are shown in Figure 2.<sup>20,57</sup> At this point, the clinical utility of these tests remains to be seen.

**Saliva:** Advantages of saliva as a test sample include the ease of collection, minimal personal invasiveness, and limited pre-analytical manipulation.<sup>3,5,58</sup> However, because drugs and/or their metabolites in saliva are generally proportional to those in plasma, they are retained for a shorter period and at lower concentrations compared with urine.<sup>5,20,57,58</sup>

**Hair:** Hair analysis provides a retrospective, long-term measure of drug use that is directly related to the length of hair.<sup>5,20,57</sup> Testing hair can extend the window of detection to weeks, months, or even years.<sup>5,59</sup> However, darkly pigmented hair has a greater capacity to bind a drug than hair that is fair or gray, leading to the claim that hair analysis might have a color bias.<sup>3,20,57</sup> Other disadvantages of hair analysis include irregular growth, accessibility of the specimen, labor-intensive sample preparation and testing, and excessive cost.<sup>3,57</sup>

**Sweat:** Sweat collection using a sweat patch is a noninvasive, cumulative measure of drug use over a period of days to weeks,<sup>20</sup> which is most appropriately used to monitor drug use in chemical dependency or probation programs.<sup>3</sup> Disadvantages include varying sweat production and risk of accidentally removing or contaminating the collection device.<sup>20</sup>

**Blood:** Blood is generally not recommended for routine testing because blood samples are not amenable to

**Figure 2. Relative detection times of drugs in various biologic specimens**



Caplan YH, Goldberger BA. *J Anal Toxicol.* 2001;25:396-399.

rapid screening procedures, have low drug concentrations and so relatively limited detection windows, and require invasive collection.<sup>3,5</sup>

### Alcohol Abstinence

Alcohol (ethyl alcohol, ethanol) is the most frequently abused drug. It can be tested in breath using a handheld device. The concentrations in breath parallel those in blood and the brain and relate to impairment. Alcohol, however, has a short duration in the body and is only detected for hours (generally less than 12) following use. Ethyl glucuronide (EtG) is a direct metabolite of alcohol formed by conjugation. While most alcohol is metabolized by alcohol dehydrogenase to carbon dioxide and water, a small portion is conjugated to EtG, a stable, nonvolatile, water-soluble substance that can persist in the urine for several days (up to 80 hours).<sup>60,61</sup> Thus EtG becomes a sensitive and specific marker to detect alcohol use, and the test has recently become commercially available. The EtG test may be useful to help motivate patients to remain or become abstinent from alcohol by providing objective evidence of abstinence, or to demonstrate abstinence when advocating for patients. The test is not useful to measure a reduction in alcohol intake.

Although alcoholic beverages contain alcohol in high concentrations, alcohol can also be found in some OTC cough products, mouthwashes, communion wine, “non-alcoholic” beer, and food. Such incidental exposure can lead to a positive EtG test even when alcoholic beverages were not consumed. There is no established cutoff concentration, and various laboratories may offer different interpretations. Generally concentrations below 100 ng/mL will require total abstinence, including the elimination of all incidental exposures. While concentrations above 1500 ng/mL are generally positive from alcoholic beverage use, concentrations below 1500 ng/mL may be the result of possible incidental exposure. More information is needed on potential causes of false-positive or -negative EtG results; for example, one study found that a urinary tract infection is a risk factor for false-negative EtG in the detection of recent alcohol consumption.<sup>62</sup> EtG test results should be used as a diagnostic aid in the total management of the patient. Healthcare professionals are cautioned that alcohol is present in many non-beverage products that can produce a positive result.

The US Department of Health and Human Services has issued a box warning which states:<sup>63</sup>

Currently, the use of an EtG test in determining abstinence lacks sufficient proven specificity for use as primary or sole evidence that an individual prohibited from drinking, in a criminal justice or a regulatory compliance context, has truly been drinking. Legal or disciplinary action based solely on a positive EtG, or other test discussed in this *Advisory*, is inappropriate and scientifically unsupported at this time. These tests should be considered as potential valuable clinical tools, but their use in forensic settings is premature.

## CONCLUSIONS

Urine drug testing can be a simple and effective tool for healthcare professionals in the assessment and ongoing management of patients who:

- Will be, or are being, treated over the long term with opioids (not for acute pain).
- Have the disease of addiction.
- Have other relevant medical conditions or diagnoses.

A working relationship with your testing laboratory or test kit provider is essential to accurately interpret UDT results. Most importantly, a healthcare professional should strive for a relationship of mutual honesty and trust with the patient when using urine drug testing in his or her clinical practice. Therefore, the use of UDTs should be consensual, be designed to help patients, and assist healthcare professionals to advocate for the health and well-being of their patients.

## CASE STUDIES IN CLINICAL PRACTICE

**Case 1:** The following case of a new patient already receiving opioid therapy is described with four potential outcomes.

**Patient Presentation:** A 47-year-old man who is new to your practice presents with severe low back pain resulting from a motor vehicle accident 3 years ago. He states that he was treated with around-the-clock morphine by his last primary care physician, who is located in the town from which he has recently relocated. He claims that the morphine regimen enables him to continue working in his position of supervisor at a local bakery. He has been taking his medication according to his treatment regimen and has only enough left for 7 more days; he wants you to continue to prescribe morphine for his low back pain. He has no self-reported history of substance misuse. You have not yet received his medical records from his previous provider to confirm his pain syndrome diagnosis and treatment regimen, but in the absence of any evidence for aberrant behavior, you want to continue his analgesic regimen with morphine.

**Question:** In addition to a thorough history and physical examination, what UDT(s) would you select to corroborate the patient's history and start to build your therapeutic alliance with the patient?

**Comment:** This new patient should be tested in a manner consistent with your normal practice prior to initial prescribing of a controlled substance. Recommended drug/drug classes to screen for in the initial immunoassay are opiates, which you would expect to be positive in this patient, and common drugs of misuse (ie, cocaine, amphetamines, methadone, marijuana, benzodiazepines, plus additional tests, as

needed) to support that the patient has not recently used unreported substances. This would be followed by the more specific GC/MS (without cutoffs) to identify the drug(s) present.

**UDT Results:** Four of the possible outcomes from urine drug testing in this patient are shown in Table 6.

1. *Immunoassay is positive only for opiates; subsequent GC/MS identifies morphine at 4000 ng/mL.*

This result supports the patient's report and history and should help to build a therapeutic relationship based on trust and honesty.

2. *Immunoassay is negative for opiates; subsequent GC/MS failed to detect morphine.*

Such a negative result requires further investigation. It suggests that the patient has not recently ingested morphine and may be consistent with diverting or trafficking drugs, but more commonly describes a bingeing pattern of drug use. Verify with the laboratory that "none detected" does mean that morphine was not detectable at the LOD, or specify "no-threshold" testing. Schedule an appointment with the patient to discuss proper medication use and to explore the possibility of diversion.

3. *Immunoassay is negative for opioids; subsequent GC/MS is positive for alternative licit opioid (eg, meperidine).*

Such a result may suggest that the patient is doctor shopping and/or misusing licit drugs. This requires further investigation to determine whether the patient has an undertreated pain syndrome (ie, pseudoaddiction) and to initiate or refer for substance misuse counseling or treatment, as indicated.

**Table 6. Four outcomes from urine drug testing in Case 1**

GC/MS results	Immunoassay results		
	Positive for opiates	Negative for opiates	Positive for other drug/drug class
1. Positive for morphine	✓		
2. Negative		✓	
3. Positive for meperidine		✓	
4. Positive for morphine & cocaine	✓		✓

#### 4. *Immunoassay is positive for opiates and cocaine; GC/MS confirms presence of morphine and cocaine.*

This result suggests that the patient may be abusing illicit drugs and may be misusing morphine. Schedule an appointment to discuss the results in order to determine whether or not the patient does have a pain syndrome. If present, this will still require treatment, but with tightening of boundaries, counseling, and consultation with/referral to a pain specialist or program experienced in the treatment of substance misuse. Continued use of cocaine, as seen with repeatedly positive UDT results, is a contraindication to long-term opioid therapy.

#### **Case 2: Adherence testing in a patient treated with oxycodone.**

**Patient Presentation:** A 35-year-old woman presents with increasing fibromyalgia pain. She initially obtained relief with oral oxycodone 40 mg per day for the past 7 months, but this regimen is no longer effective and her pain is now continuous. Before increasing the dose of oxycodone, you want to order a UDT to help support and document that she is, in fact, adherent to her current regimen.

**Question:** What UDT(s) would you select to support that the patient is adherent to her current regimen of oxycodone?

**Comment:** The routine detection of oxycodone (a semisynthetic opioid) by opiate immunoassay (designed to detect morphine and codeine) is notoriously difficult. Even large concentrations of oxycodone in the urine may not be detected, although positive results may occur because of cross-reactivity. To monitor adherence with oxycodone (or other synthetic/semisynthetic opioid), order a GC/MS or HPLC without cutoff (LOD), which will detect and accurately identify oxycodone, when present.

#### **Case 3: Adherence testing in a patient prior to switching opioid analgesics.**

**Patient Presentation:** A 39-year-old male truck driver presents with increasing low back pain. Following his initial presentation for low back pain 18 months ago with a pain score of 8/10, he was treated with modified-release morphine 15 mg bid, which was

increased to 30 mg bid after 3 weeks. This regimen provided some relief of his pain, which decreased to a level of 5-6/10. However, trials of increasing the morphine dose in an attempt to improve pain management resulted in unacceptable side effects. You decide to rotate to an alternative opioid and select hydromorphone. Prior to making the switch, you perform a UDT using a GC/MS pain panel that your laboratory offers—this tests for morphine, codeine, hydrocodone, hydromorphone, and oxycodone—in order to corroborate and document in the medical record the patient's adherence to his current opioid regimen. You expect the UDT to be positive for morphine and negative for all other opioids.

**UDT Result:** The UDT comes back positive for morphine as expected and hydromorphone unexpectedly. On the basis of such a result you believe that the patient may have been obtaining hydromorphone from the “street” or another clinician without your knowledge. However, when you discuss the results with your laboratory director, he informs you that hydromorphone may be a metabolite of morphine, and it was detected at a concentration of about 15% compared to morphine. This result—a positive for both the parent drug and lower levels of a potential metabolite—supports adherence to the drug regimen rather than indicating aberrant behavior. An interview with the patient confirms your interpretation. Therefore, you switch to a trial of hydromorphone to see if the patient's pain management is improved with this opioid.

**Comment:** If the UDT result had come back positive only for hydromorphone or with equal/greater concentration of hydromorphone, however, it would not have been consistent with the patient taking his current regimen of morphine alone, and would suggest the addition of an unprescribed opioid. This would merit further investigation with the laboratory and the patient to ensure that the patient has not been taking hydromorphone.

## APPENDIX

### REIMBURSEMENT

The CPT codes for qualitative drug tests are as follows:

- Procedure code 80100: a qualitative drug screen that is performed to detect the presence of multiple drug classes.
- Procedure code 80101: a qualitative drug screen that is performed to detect the presence of a single drug class (if the presence of more than one drug class is suspected, use 80100).
- Procedure code 80102: each procedure necessary to confirm the presence of a drug(s) (eg, GC/MS, HPLC).

An ICD-9 code may also have to be recorded to establish the “medical necessity” of each service. Although a number of ICD-9 codes support medical necessity for UDTs (eg, unspecified drug dependence, drug misuse, active treatment for substance misuse), insurers may not deem a qualitative drug test necessary when the clinical picture is consistent with the reported history. Medical record documentation maintained by the ordering healthcare professional should indicate the medical necessity for performing a qualitative drug test and a copy of the laboratory results should be maintained in the medical records.

Insurance coverage will be individual to each patient’s policy/plan.

The average list price for a 6-panel immunoassay (cocaine, amphetamines, opiates, methadone, marijuana, benzodiazepines) is approximately \$15. The cost of specific drug identification (eg, GC/MS) is approximately \$25 to \$40. The cost of tests will vary according to volume of testing and negotiated terms of any account held with the laboratory.

### ABBREVIATIONS

<b>AIDS</b>	acquired immunodeficiency syndrome
<b>CNCP</b>	chronic noncancer pain
<b>CNS</b>	central nervous system
<b>CPT</b>	Current Procedural Terminology
<b>DOT</b>	Department of Transportation
<b>DEA</b>	Drug Enforcement Administration
<b>EtG</b>	ethyl glucuronide
<b>GC</b>	gas chromatography
<b>GC/MS</b>	gas chromatography/mass spectrometry
<b>HPLC</b>	high-performance liquid chromatography
<b>ICD-9</b>	International Classification of Diseases
<b>LOD</b>	limit of detectability
<b>6-MAM</b>	6-monoacetylmorphine
<b>MET</b>	motivational enhancement therapy
<b>MS</b>	mass spectrometry
<b>ORT</b>	Opioid Risk Tool
<b>OTC</b>	over-the-counter
<b>PCP</b>	phencyclidine
<b>POC</b>	point-of-care
<b>SAMHSA</b>	Substance Abuse and Mental Health Services Administration
<b>THC</b>	11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid
<b>THCA</b>	11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid
<b>UDT</b>	urine drug test

## GLOSSARY

**addiction** A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

**adherence testing** Assessment of a patient's adherence to a treatment plan, typically looking for the presence of prescribed medications.

**adulteration panel** Method to determine the characteristics of urine (eg, specific gravity, creatinine level) and to check for the presence of common adulterants. Most laboratories that do routine drug testing are familiar with tests for adulteration.

**analyte** Any material or chemical substance subjected to analysis.

**chain of custody** A legal term that refers to the ability to guarantee the identity and integrity of the specimen from collection through to reporting of the test results.

**cutoff** The drug concentration above which an assay reports a positive result and below which the result is negative.

**dilute** A urine specimen that has a creatinine concentration less than 20 mg/dL.

**diversion** Diverting drugs from their lawful medical purpose.

**“Federal Five”** The drugs/drug classes that are tested for in federal employees and federally regulated industries.

**GC** Gas chromatography, a procedure to separate the different components within a specimen.

**GC/MS** A combination of two techniques; gas chromatography is used to separate the different components in a specimen, and mass spectrometry is used to specifically identify the components of the specimen.

**isomer** One of two or more substances that exist in forms that are identical with respect to composition, but differ in the positions of one or more atoms within the molecules, as well as in physical and chemical properties.

**LOD** Limit of detection, or lowest amount of drug that a laboratory can reliably identify in a specimen. The limit of detection varies depending on the methodology and laboratory.

**6-MAM** 6-monoacetylmorphine, a metabolite of heroin.

**MET** Motivational enhancement therapy, a patient-centered counseling approach for initiating behavior change by helping patients to resolve ambivalence about engaging in treatment and stopping drug use.

**MS** Mass spectrometry, a procedure to very specifically identify the components of a specimen.

**opiate** An historical term restricted to naturally occurring alkaloids derived from opium (morphine, codeine, thebaine).

**opioid** A more current term that includes opiates and synthetic/semisynthetic agents that exert their effects by binding to highly selective opioid receptors.

**physical dependence** A state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

**point-of-care testing** On-site testing using commercial devices without the need for instrumentation.

**pseudoaddiction** The iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain management.

**recovery program** An ongoing process to help the patient develop coping strategies and tools for abstaining from drug use and then maintaining abstinence.

**split sample** Splitting a single urine void into two separate bottles labeled A and B; bottle A is tested and bottle B remains sealed and available for testing at the direction of the donor. Mandatory in some federal drug testing programs.

**substance misuse (abuse)** A precise definition for substance misuse has not been established; however, a working definition is the use of any substance that harms or endangers the individual, family, or community in an individual who does not meet the criteria for addiction to that substance.

**trafficking** Unlawful transfer of controlled drugs.

**Universal Precautions** Recommendations to guide patient assessment, management, and referral to improve patient care, reduce stigma, and contain risk.

## REFERENCES

- Hammett-Stabler CA, Pesce AJ, Cannon DJ. Urine drug screening in the medical setting. *Clin Chim Acta*. 2002;315:125-135.
- Galloway JH, Marsh ID. Detection of drug misuse—an addictive challenge. *J Clin Pathol*. 1999;52:713-718.
- Wolff K, Farrell M, Marsden J, et al. A review of biological indicators of illicit drug use, practical considerations and clinical usefulness. *Addiction*. 1999;94:1279-1298.
- Casavant MJ. Urine drug screening in adolescents. *Pediatr Clin North Am*. 2002;49:317-327.
- Braithwaite RA, Jarvie DR, Minty PS, et al. Screening for drugs of abuse. I: Opiates, amphetamines and cocaine. *Ann Clin Biochem*. 1995;32(Pt 2):123-153.
- Passik SD, Schreiber J, Kirsh KL, Portenoy RK. A chart review of the ordering and documentation of urine toxicology screens in a cancer center: do they influence patient management? *J Pain Symptom Manage*. 2000;19:40-44.
- Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6:107-112.
- Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27:260-267.
- Brasseux C, D'Angelo LJ, Guagliardo M, Hicks J. The changing pattern of substance abuse in urban adolescents. *Arch Pediatr Adolesc Med*. 1998;152:234-237.
- Yang JM. Toxicology and drugs of abuse testing at the point of care. *Clin Lab Med*. 2001;21:363-74,ix-x.
- Shults TF. The Medical Review Officer Handbook. 8th ed. North Carolina: Quadrangle Research, LLC; 2002.
- Code of Federal Regulations. 49 CFR §40. Office of the Federal Register. 1998. Available at: <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html>.
- Simpson D, Braithwaite RA, Jarvie DR, et al. Screening for drugs of abuse (II): Cannabinoids, lysergic acid diethylamide, buprenorphine, methadone, barbiturates, benzodiazepines and other drugs. *Ann Clin Biochem*. 1997;34(Pt 5):460-510.
- Office of National Drug Control Policy. What You Need to Know About Drug Testing in Schools. 2002. Available at: [http://www.whitehousedrugpolicy.gov/pdf/drug\\_testing.pdf](http://www.whitehousedrugpolicy.gov/pdf/drug_testing.pdf).
- Perrone J, De Roos F, Jayaraman S, Hollander JE. Drug screening versus history in detection of substance use in ED psychiatric patients. *Am J Emerg Med*. 2001;19:49-51.
- Hattab EM, Goldberger BA, Johannsen LM, et al. Modification of screening immunoassays to detect sub-threshold concentrations of cocaine, cannabinoids, and opiates in urine: use for detecting maternal and neonatal drug exposures. *Ann Clin Lab Sci*. 2000;30:85-91.
- Adams NJ, Plane MB, Fleming MF, et al. Opioids and the treatment of chronic pain in a primary care sample. *J Pain Symptom Manage*. 2001;22:791-796.
- Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6:432-442.
- Schnoll SH, Finch J. Medical education for pain and addiction: making progress toward answering a need. *J Law Med Ethics*. 1994;22:252-256.
- Caplan YH, Goldberger BA. Alternative specimens for workplace drug testing. *J Anal Toxicol*. 2001;25:396-399.
- Katz NP. Behavioral monitoring and urine toxicology testing in patients on long-term opioid therapy. Presented at the American Academy of Pain Medicine 17th Annual Meeting; February 14, 2001; Miami Beach, Florida.
- Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg*. 2003;97:1097-1102, table.
- Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *J Pain Symptom Manage*. 1996;11:203-217.
- Katz N, Fanciullo GJ. Role of urine toxicology testing in the management of chronic opioid therapy. *Clin J Pain*. 2002;18(4 Suppl):S76-S82.
- Savage SR. Assessment for addiction in pain-treatment settings. *Clin J Pain*. 2002;18(4 Suppl):S28-S38.
- Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and "problematic" substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage*. 1998;16:355-363.
- Weissman DE, Haddox JD. Opioid pseudoaddiction—an iatrogenic syndrome. *Pain*. 1989;36:363-366.
- Heit HA, Gourlay D. Pain and addiction: managing risk through comprehensive care. Submitted for publication 2006.
- The Federation of State Medical Boards of the United States Inc. Model Policy for the Use of Controlled Substances for the Treatment of Pain. 2004. Available at: <http://www.fsmb.org>.
- Code of Federal Regulations. 21 CFR§1306.07. Office of the Federal Register. 2004. <http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200421>.
- Heit HA. Federal regulations for prescribing a scheduled controlled substance: update – 10/01/03. American Society of Addiction Medicine. 2003. Available at: [http://www.asam.org/pain/federal\\_regulations\\_for\\_prescrib.htm](http://www.asam.org/pain/federal_regulations_for_prescrib.htm).
- Heit HA. Creating and implementing opioid agreements. *Disease Management Digest*. 2003;7:2-3.
- Savage S, Covington E, Gilson AM, et al. Public policy statement on the rights and responsibilities of healthcare professionals in the use of opioids for the treatment of pain. A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. 2004. Available at: <http://www.asam.org/ppol/opioids.htm>.
- Heit HA, Covington E, Good PM, Dear DEA. *Pain Med*. 2004;5:303-308.
- George S, Braithwaite RA. Use of on-site testing for drugs of abuse. *Clin Chem*. 2002;48:1639-1646.
- Vandevenne M, Vandebussche H, Verstraete A. Detection time of drugs of abuse in urine. *Acta Clin Belg*. 2000;55:323-333.
- Cook JD, Caplan YH, LoDico CP, Bush DM. The characterization of human urine for specimen validity determination in workplace drug testing: a review. *J Anal Toxicol*. 2000;24:579-588.
- Code of Federal Regulations. 49 CFR §40. DHHS NLCP Program Document (PD) #035. Office of the Federal Register. 1998. Available at: <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html>.
- Von Seggern RL, Fitzgerald CP, Adelman LC, Adelman JU. Laboratory monitoring of OxyContin (oxycodone): clinical pitfalls. *Headache*. 2004;44:44-47.
- Baden LR, Horowitz G, Jacoby H, Eliopoulos GM. Quinolones and false-positive urine screening for opiates by immunoassay technology. *JAMA*. 2001;286:3115-3119.
- Zacher JL, Givone DM. False-positive urine opiate screening associated with fluoroquinolone use. *Ann Pharmacother*. 2004;38:1525-1528.
- Neogen Corporation. Forensic drug detection ELISA kit cross-reactivity data. 2006.
- Bond GR, Steele PE, Uges DR. Massive venlafaxine overdose resulted in a false positive Abbott AxSYM urine immunoassay for phencyclidine. *J Toxicol Clin Toxicol*. 2003;41:999-1002.
- Sena SF, Kazimi S, Wu AH. False-positive phencyclidine immunoassay results caused by venlafaxine and O-desmethylvenlafaxine. *Clin Chem*. 2002;48:676-677.
- Rohrig TP, Moore C. The determination of morphine in urine and oral fluid following ingestion of poppy seeds. *J Anal Toxicol*. 2003;27:449-452.
- Inturrisi CE, Max MB, Foley KM, et al. The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med*. 1984;310:1213-1217.
- Cone EJ, Heit HA, Caplan YH, Gourlay D. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine. *J Anal Toxicol*. 2006;30:1-5.
- Oyler JM, Cone EJ, Joseph RE, Jr., Huestis MA. Identification of hydrocodone in human urine following controlled codeine administration. *J Anal Toxicol*. 2000;24:530-535.
- Heit HA, Gourlay DL, Caplan YH. Personal communication. 2004.
- Chen YL, Hanson GD, Jiang X, Naidong W. Simultaneous determination of hydrocodone and hydromorphone in human plasma by liquid chromatography with tandem mass spectrometric detection. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2002;769:55-64.
- Levy S, Harris SK, Sherritt L, et al. Drug testing of adolescents in ambulatory medicine: physician practices and knowledge. *Arch Pediatr Adolesc Med*. 2006;160:146-150.
- EISOHLY MA, deWit H, Wachtel SR, et al. Delta9-tetrahydrocannabinol as a marker for the ingestion of marijuana versus Marinol®: results of a clinical study. *J Anal Toxicol*. 2001;25:565-571.
- Gourlay D. Addiction and pain medicine. *Pain Res Manag*. 2005;10(Suppl A):38A-43A.
- Wyeth-Ayerst. PROTONIX® (pantoprazole sodium) Package Insert. 2005.
- Leson G, Pless P, Grotenhermen F, et al. Evaluating the impact of hemp food consumption on workplace drug tests. *J Anal Toxicol*. 2001;25:691-698.
- Bosy TZ, Cole KA. Consumption and quantitation of delta9-tetrahydrocannabinol in commercially available hemp seed oil products. *J Anal Toxicol*. 2000;24:562-566.
- Kintz P, Samyn N. Use of alternative specimens: drugs of abuse in saliva and doping agents in hair. *Ther Drug Monit*. 2002;24:239-246.
- Yacoubian GS, Jr., Wish ED, Perez DM. A comparison of saliva testing to urinalysis in an arrestee population. *J Psychoactive Drugs*. 2001;33:289-294.
- Kintz P, Villain M, Cirimele V. Hair analysis for drug detection. *Ther Drug Monit*. 2006;28:442-446.
- Bergstrom J, Helander A, Jones AW. Ethyl glucuronide concentrations in two successive urinary voids from drinking drivers: relationship to creatinine content and blood and urine ethanol concentrations. *Forensic Sci Int*. 2003;135:86-94.
- Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide—the direct ethanol metabolite on the threshold from science to routine use. *Addiction*. 2003;98(Suppl 2):51-61.
- Helander A, Dahl H. Urinary tract infection: a risk factor for false-negative urinary ethyl glucuronide but not ethyl sulfate in the detection of recent alcohol consumption. *Clin Chem*. 2005;51:1728-1730.
- Center for Substance Abuse Treatment. The role of biomarkers in the treatment of alcohol use disorders. *Substance Abuse Treatment Advisory*. 2006;5(4):1-8.

## EVALUATION: URINE DRUG TESTING IN CLINICAL PRACTICE

We would like your opinion regarding this educational activity. Please complete this evaluation form and mail or fax it, along with your CME registration form and answers to the self-assessment questions, as indicated on page 24.

**1. Approximately how long did it take you to complete this educational activity?**

1.5 hours     Other

**2. As a result of completing this activity, are you now better able to:**

**Objective 1:** Clarify the purpose of urine drug testing and identify a clear testing strategy.

Yes     No     Somewhat

**Objective 2:** Distinguish between urine drug testing for detection of illicit drug use and for monitoring adherence to a treatment regimen.

Yes     No     Somewhat

**Objective 3:** Describe drug testing methodology, instrumentation, and sensitivity/specificity of results.

Yes     No     Somewhat

**Objective 4:** Highlight strategies to improve analysis and interpretation of results.

Yes     No     Somewhat

**Objective 5:** Understand the limitations of urine drug testing.

Yes     No     Somewhat

**3. Were the teaching resources effective in presenting this content?**

Yes     No     Somewhat

**4. Was the content of this activity clearly written?**

Yes     No     Somewhat

**5. Was the content free from commercial bias and promotion?**

Yes     No     Somewhat

**6. What changes, if any, will you make in your practice as a result of this activity?**

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## SELF-ASSESSMENT QUESTIONS: URINE DRUG TESTING IN CLINICAL PRACTICE

- 1. What is the window of detection of most drugs in urine?**
  - a. 1 to 3 hours.
  - b. 6 to 12 hours.
  - c. 1 to 3 days.
  - d. 6 to 9 months.
- 2. Immunoassays can:**
  - a. Identify a specific drug or drug metabolite.
  - b. Detect the presence of a drug class.
  - c. Provide quantitative results.
  - d. Be performed only in a testing laboratory.
- 3. GC/MS can:**
  - a. Be performed at POC, without the need for instrumentation.
  - b. Identify a specific drug or drug metabolite.
  - c. Detect only drugs that are recognized by immunoassays.
  - d. Be affected by cross-reactivity.
- 4. A specimen consistent with normal human urine has a creatinine concentration:**
  - a. Between 5 and 20 mg/dL.
  - b. Greater than 20 mg/dL.
  - c. Less than 5 mg/dL.
- 5. Most opiate immunoassays, which are designed to detect morphine and codeine, do not reliably detect synthetic or semisynthetic opioids.**
  - a. True.
  - b. False.
- 6. A prescription for morphine can explain the presence of codeine in urine.**
  - a. True.
  - b. False.
- 7. A urine drug test can be used to determine:**
  - a. The dose of drug taken.
  - b. Presence of a drug or drug metabolite.
  - c. Time of last dose.
  - d. Source of the drug.
- 8. An immunoassay negative for opiates in a patient who is being prescribed oxycodone indicates that the patient:**
  - a. Has not recently taken morphine or codeine; use GC/MS to detect presence of oxycodone, asking for “no threshold” testing to detect low levels.
  - b. Has not recently taken any opioids, including oxycodone, morphine, and codeine, which is consistent with diverting or trafficking prescribed drugs.
- 9. A GC/MS positive for morphine and hydromorphone in a patient who is being prescribed morphine is consistent with the patient:**
  - a. Obtaining hydromorphone from the “street” or another clinician.
  - b. Taking only morphine, if the concentration of hydromorphone is less than that of morphine.
  - c. Taking morphine alone, regardless of the relative concentrations of the two drugs.
- 10. A UDT for EtG is useful clinically to:**
  - a. Support alcohol abstinence.
  - b. Encourage a reduction in alcohol intake.



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