

Urine Drug Testing in Clinical Practice



*The Art
and Science
of Patient
Care*

■■■■ EDITION 4



Target Audience: Family physicians and other primary care physicians



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NEEDS STATEMENT

Urine drug testing (UDT) encompasses a variety of tests that can be very useful in patient care. For example, UDT can be used to document adherence to the agreed-upon treatment plan, to aid in the diagnosis of drug addiction or diversion, or for patient advocacy.

In 2009, the American Pain Society and the American Academy of Pain Medicine convened an expert panel that developed Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain.* The panel concluded that UDT has a central role in monitoring patients receiving chronic opioid therapy to avoid its potential harms. Specifically, the panel recommended that UDT should be used periodically in all treated patients who are at high risk for abuse or diversion, and that UDT should also be considered even for patients who do not have known risk factors in order to confirm adherence to the chronic opioid therapy plan of care. In our opinion, UDT should be considered in all patients, including those without apparent elevated risk, as part of the protocol of practices, especially when controlled substances, such as opioids, are prescribed. The literature is clear that when aberrant behavior alone is used as a trigger for UDT, a significant proportion of patients who would benefit from this technology will be missed.† Therefore, a consistent clinical approach in performing UDT will optimize the use of this technology for both patient and practitioner alike.

Clinicians often lack training in the appropriate use of UDT. Because of this, UDT is often underused or used inappropriately in clinical care. Determining the appropriate use of UDT can involve complex decision-making processes. Before ordering UDT, clinicians should be clear about their reasons for using it, as well as its potential benefits, limitations, and challenges related to interpretation of results. Ideally, UDT should be done as part of a consensual process between clinicians and patients, with full explanation to and for the benefit of the patient.

This monograph provides clinicians with the necessary knowledge to incorporate UDT into clinical practice, with an emphasis on its use as a safety and monitoring tool for patients who are being prescribed opioids for chronic pain.

LEARNING OBJECTIVES

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

1. Determine appropriate uses of UDT for individual patients in different clinical situations
2. Distinguish between the use of UDT for monitoring adherence to therapy and for detection of illicit or unprescribed drug use
3. Differentiate between different UDT methodologies and their appropriate clinical applications
4. Formulate strategies to improve usefulness and accurate interpretation of UDT results
5. Describe the strengths and limitations of UDT in clinical practice
6. Decide when to seek expert assistance with interpretation of results
7. Compare the applications of drug testing that are not urine-based

GOAL

This document is designed to provide clinicians with an understanding of the appropriate uses of UDT in clinical practice, with a primary goal of using UDT as a tool to improve the clinical care and outcomes for patients, especially those who are prescribed chronic opioids or other controlled substances as a part of their routine clinical care, and to assist in interpretation of clinical conundrums.

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3. Upon successful completion of the requirements, you will be mailed a CME certificate within 4 to 6 weeks.

*Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guideline Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113-130.

†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.

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FOREWORD

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The long-term administration of opioid drugs to patients with chronic pain is a standard of care in populations with active cancer or other advanced illness, and is widely viewed as a potentially effective treatment in a carefully selected subgroup with chronic pain of other causes. In many developed countries, including the United States, opioid prescription for chronic pain has increased manyfold during the past 3 decades. The positive implication of these data—that patients with pain are gaining access to effective therapy—has been balanced by the very troubling evidence that rising prescription drug abuse has paralleled the increase in legitimate use. This observation has driven a fundamental change in the clinical approach to the use of opioids and other potentially abusable drugs. Clinicians have a responsibility to bring “balance to the bedside” by incorporating best practices in risk management with thoughtful strategies to ensure appropriate patient selection for opioid therapy and optimal administration once treatment is begun. Only in this way can clinicians meet a dual obligation to promote patient well-being by recognizing, assessing, and managing pain, while concurrently minimizing the adverse outcomes associated with the use of an abusable drug.

Safe prescribing now requires expertise in approaches that minimize the risk of unintentional overdose, drug abuse, addiction, and diversion. These approaches include urine drug testing, and while there is yet no consensus among pain specialists about the patients who should be tested and how often to test, there is broad and unqualified agreement that clinicians who treat patients with opioid drugs should be able to use urine drug testing as a tool in the assessment of drug-related behavior. There also is agreement that urine drug testing, like all tests, will yield useless information unless the indications, practicalities, and interpretation of the data are appreciated by those who order it. These details are addressed in this excellent monograph. The information it contains is accurate and accessible, and should be embraced by every clinician who is seeking to improve skills in risk management during opioid therapy for chronic pain.

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BACKGROUND

The traditional clinical role of urine drug testing (UDT) has been to support treatment decisions made in the urgent care setting where patients are unable or, in some cases, unwilling to provide information about the use of substances that may be harmful to them.^{1,2} When used effectively, however, UDT is more than just a verification tool and has many useful clinical applications in patient-centered testing. This monograph serves to address some of the issues surrounding UDT, to describe why the use of UDT is at once (1) more complex and (2) potentially more useful than many clinicians appreciate, and to assist clinicians to pursue UDT further in their practices using a clear testing strategy.

The most common uses of UDT have involved forensic testing in federally regulated industries (eg, Department of Transportation) and nonregulated forensic testing outside the federal system. *Forensic UDT* generally assumes that the majority of donors will be negative for substances that may have misuse liability. In contrast, in *patient-centered UDT* the majority of donors are in fact positive for the drug(s) of interest since these are often prescribed for legitimate medical purposes. This can add to the complexity of interpretation, which will be discussed throughout the document.

The term urine drug “screening” is a misnomer since it implies screening for all drugs.^{1,3} In reality, it is not possible to prove the presence or absence of all drugs, and the testing process is open-ended and evolving.⁴ No “standard” UDT is suitable for all purposes and settings—rather, a multitude of options exists that health care professionals should adapt to their particular clinical needs.¹ The 3 main types of UDT are:

- 1. Immunoassay drug testing**
Either laboratory based or at point-of-care* (POC), eg, “dip-stick” testing
- 2. Laboratory-based specific drug identification**
eg, gas chromatography/mass spectrometry[†] (GC/MS) or liquid chromatography/mass spectrometry[‡] (LC/MS)
- 3. Comprehensive combination of techniques**
eg, special applications for pain testing

UDT typically detects the parent drug and/or its metabolite(s) and, therefore, demonstrates recent use of prescription medications and illegal substances.^{1,5,6} Although other biologic specimens can be used in drug testing, urine is usually preferred for determining the presence or absence of drugs because it has a 1- to 3-day window of detection for most drugs and/or their metabolites and is currently the most extensively validated biologic specimen for drug testing. Technologies for alternative specimen drug testing are briefly reviewed on pages 14-15.^{5,7}

This monograph will help clinicians in deciding when to order UDT and the type of UDT to order for an individual patient, as well as provide advice for interacting with the testing laboratory to ensure that the clinical needs are being met.

*Point-of-care testing (POC): on-site testing using commercial devices without the need for instrumentation

†Gas chromatography/mass spectrometry (GC/MS): 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

‡Liquid chromatography/mass spectrometry (LC/MS): liquid chromatography is used to separate the different components in a specimen, and mass spectrometry is used to specifically identify the components of the specimen

URINE DRUG TESTING METHODS

For most clinical and forensic applications, initial testing is often done with class-specific immunoassay drug panels, which are designed to classify substances as either present or absent according to predetermined cutoff* thresholds. Definitive identification of a specific drug and/or its metabolite(s) requires more sophisticated tests, such as GC/MS or LC/MS. The UDT method chosen should be a function of the question that needs to be answered.

IMMUNOASSAYS

The immunoassay drug tests, which are designed to classify substances as either present or absent according to a predetermined cutoff threshold, are the most common methods. Immunoassays are based on the principle of competitive binding, and use antibodies to detect the presence of a particular drug or metabolite in a urine sample.⁸ 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. The principal disadvantage is that immunoassays 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's 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;⁸ ie, substances with similar, and sometimes dissimilar, chemical composition may cause a test to appear positive for the target drug (see pages 9-10 for more details). Samples that test positive by immunoassay for classes of drug may need to be tested in the laboratory by an alternative method if specific identification of the drug is required.

Point-of-Care Testing

A number of single-use immunoassay devices are commercially available for POC UDT of common classes of misused drugs. POC devices typically use immunochromatographic methods that produce visually read results.⁹ However, POC testing by immunoassay in isolation is often inadequate in patient-centered UDT 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. 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.⁹ 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.

*Cutoff: the drug concentration above which an assay reports a positive result and below which the result is negative

†Opiate: historical term restricted to naturally occurring alkaloids derived from opium (morphine, codeine, thebaine)

POC devices have a rapid turnaround time, are portable, and are seemingly easy to use, but still require proficiency to produce acceptable performance.⁹⁻¹² 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, cost, a limited menu of drugs offered, and lack of evidence that using POC devices improves patient outcomes when compared with laboratory testing.^{12,13} Training of users should include quality issues and recognition of any device limitations.¹² In contrast to testing laboratories, POC devices purchased from a manufacturer may not include independent scientific support, although most manufacturers offer a toll-free "hot-line" for consultation. Therefore, the clinician should evaluate carefully a POC device before routine use and utilize such devices with caution to prevent misinterpretation of the results generated. A particularly useful role for POC testing is to identify illicit drug use in a timely fashion.

LABORATORY-BASED SPECIFIC DRUG IDENTIFICATION

Generally, a more definitive laboratory-based procedure (eg, GC/MS, LC/MS) to identify specific drugs is needed in 3 instances: (1) to specifically confirm the presence of a given drug; for example, that morphine is the opiate[†] causing the positive immunoassay response; (2) to identify drugs not included in an immunoassay test; and (3) when results are contested.

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.¹⁴ Although governed by various factors, including dose, route of administration, metabolism, fat solubility, urine volume, and pH, the detection time of most drugs in urine is 1 to 3 days (Table 1).^{15,16} Long-term use of lipid-soluble drugs such as marijuana, diazepam, ketamine, or phencyclidine (PCP) may extend the window of detection to a week or more.

Table 1. Approximate windows of detection of drugs in urine

Drug	Detection time in urine
Amphetamines	Up to 3 days
THC (depending on the grade and frequency of marijuana use) – Single use – Chronic use	– 1 to 3 days – Up to 30 days
Benzoylcegonine after cocaine use	2 to 4 days
Opiates (morphine, codeine)	2 to 3 days
Methadone – EDDP (methadone metabolite)	Up to 3 days – Up to 6 days
Benzodiazepines (depending on specific agent and quantity used)	Days to weeks

EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine;
THC=delta-9-tetrahydrocannabinol

CHARACTERISTICS OF URINE

The characterization of a urine specimen* is based on its appearance, temperature, pH, urinary creatinine concentration, and specific gravity.^{8,17} The color of a urine specimen is related to the concentration of its constituents. Concentrated urine samples are generally 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.[†] Urine can appear colorless as a result of excess hydration due to diet, medical condition, or deliberate 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 samples are 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 if the sample is of sufficient volume (30 mL or more).¹⁷ Urinary pH undergoes physiologic fluctuations throughout the day, but should remain within the range of 4.5 to 8.0.¹⁷ Sample degradation, due to improper storage or prolonged transportation, even in the absence of sample adulteration, can result in sample pH in excess of 9.0.¹⁸ Urinary creatinine varies with state of daily water intake and hydration.¹⁷ A specimen consistent with normal human urine has a creatinine concentration greater than 20 mg/dL.¹⁹ A specimen is considered dilute when the creatinine is less than 20 mg/dL and the specific gravity is less than 1.003.²⁰ A creatinine concentration less than 2 mg/dL is not consistent with human urine. Federally regulated testing programs have additional criteria for creatinine ranges between 2 and 19 mg/dL.²⁰ Aberrant test results should be discussed with the patient and/or the laboratory, as necessary.

Specimen Collection

The purpose of UDT in the clinical context, in which the vast majority of patients are not going to tamper with their urine samples, is to enhance patient care. However, certain things can be done to improve the reliability of the results obtained, including attention to the temperature, volume, and visual inspection of the sample color.³ An unusually hot or cold specimen, small sample volume, or unusual color should raise concerns. If tampering is suspected, the sample should not be discarded, but a second sample should be collected and both sent for analysis. Laboratories keep specimens for a variable period of time; check with the laboratory before testing to insure specimens are available and maintained should additional testing be required for both negative and positive results.

Table 2. Initial and confirmatory cutoff concentrations used for federally regulated testing (proposed [effective May 1, 2010])²⁰

Initial test analyte	Initial test cutoff (ng/mL)	Confirmatory test analyte	Confirmatory test cutoff (ng/mL)
Marijuana metabolites	50	THCA	15
Cocaine metabolites	300	Benzoylcegonine	150
Opiate metabolites		Codeine	2000
• Codeine/morphine ^a	2000	Morphine	2000
• 6-MAM	10	6-MAM	10
Phencyclidine	25	Phencyclidine	25
Amphetamines		Amphetamine	250
• Amphetamine/methamphetamine ^b	500	Methamphetamine ^c	250
• MDMA	500	MDMA	250
		MDA	250
		MDEA	250

THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid; 6-MAM=6-monoacetylmorphine; MDMA=methylenedioxyamphetamine; MDA=methylenedioxyamphetamine; MDEA=methylenedioxyethylamphetamine

^aMorphine is the target analyte for codeine/morphine testing.

^bMethamphetamine is the target analyte for amphetamine/methamphetamine testing.

^cTo be reported positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to or greater than 100 ng/mL.

CURRENT USES OF URINE DRUG TESTING

Though forensic UDT is usually not performed by primary care clinicians, it is the most common use of UDT. It will be briefly described here in order to inform health care professionals of issues that may come up in the course of usual care or in the course of UDT performed for other reasons.

FEDERALLY REGULATED TESTING

The “Federal Five” drugs or drug classes that are tested for in federal employees and federally regulated industries are marijuana, cocaine, opiates, PCP, and amphetamines/methamphetamines.^{8,20,21} Recent revisions to the Mandatory Guidelines for Federal Workplace Drug Testing Programs incorporate tests for a broader range of illicit substances, including the expanded “designer” amphetamine class:²⁰

- 3,4-methylenedioxyamphetamine (MDMA, “Ecstasy,” or “Adam”)
- 3,4-methylenedioxyamphetamine (MDA or “Love Drug”)
- 3,4-methylenedioxyethylamphetamine (MDEA or “Eve”)

Positive results based on immunoassays alone are referred to as “presumptive positives” by authorities because of factors such as cross-reactivity and different sensitivity and specificity between immunoassays.⁸ In the federal model, the results must be confirmed by a more specific method such as GC/MS or LC/MS.²⁰ The split sample* and chain of custody† requirements for federally regulated testing are not typically applicable to clinical practice. **Table 2** shows the most recent federally mandated immunoassay screening and confirmation cutoff concentrations for the Federal Five. Details of the federal program are beyond the scope of this monograph, but it should be noted that the cutoff concentrations used for drugs in federally regulated testing, particularly opioids,‡ are too high to be of value in clinical practice.

NONREGULATED FORENSIC TESTING

Nonregulated forensic UDT is used for a growing range of purposes, many of which have possible legal implications. Examples include 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; school children participating in competitive extracurricular activities; and random workplace testing.^{4,22,23} Such nonregulated testing may require a chain of custody, split samples, and secure storage of non-negative test specimens.²² Clinicians should stay within their scope of practice and be cautious about allowing clinical UDT results to be used in forensic settings.

The scope of nonregulated testing often includes drugs beyond those listed in the Federal Five; other drugs for which immunoassays are available include methadone, propoxyphene, benzodiazepines, oxycodone, and barbiturates, with more being added continually.^{3,8}

PATIENT-CENTERED CLINICAL URINE DRUG TESTING

In contrast to forensic UDT, which generally assumes that the majority of donors will be negative for substances that may have misuse liability, in clinical testing for therapeutic purposes the vast majority of donors are in fact positive for the drug(s) of interest since these are often prescribed for legitimate medical purposes.²⁴ Controversies exist regarding the clinical value of UDT, partly because most current methods are designed for, or adapted from, forensic or workplace deterrent-based testing for illicit drug use.¹ As a result, these methods are rarely optimized for clinical applications for which a number of licit prescription drugs must also be included. When used with an appropriate level of understanding, however, UDT can improve a clinician’s ability to manage therapy with prescription drugs (including controlled substances), to assist in the diagnosis of substance misuse⁵ or addiction,¹¹ to guide treatment, and to advocate for patients.^{1,5,24-27} For example, UDT is often used, together with an appropriate history and physical examination, to support treatment decisions made in urgent care settings (eg, when the patient is reported to have misused substances, presents a variety of certain symptoms, or has experienced trauma).^{1,2} Chemical-dependency programs regularly perform UDT to monitor patients’ adherence to maintenance drugs, to reinforce behavioral change, and to direct appropriate further treatment.¹ Other clinical uses include testing prior to medical procedures and testing pregnant women at risk for substance misuse or addiction.^{1,28}

The remainder of this monograph will focus on UDT used to assist in monitoring adherence to a controlled substance treatment regimen (eg, for chronic noncancer pain),^{25,26,29} and to identify drug misuse or addiction prior to starting or during treatment with controlled substances. Just as clinicians use hemoglobin A1c to identify hyperglycemia and as an objective measure of diabetes treatment success, the clinician can use a discordant UDT result to motivate change on the part of the patient.²⁹ Testing cannot, however, substitute for diagnostic skills or an ongoing therapeutic alliance with a patient.¹⁵ 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.

UDT is generally underused and, when used, is often used incorrectly 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 UDT and, when they did use it, the results were not documented appropriately to indicate clinical utility.³⁰ Another survey among family physicians found that those who order UDT to monitor their patients on chronic opioid therapy were not proficient in their interpretation of the results.³¹ The appropriate use of UDT as one of several medical management tools (eg, treatment agreements, pain scales, querying state prescription monitoring programs [PMPs]) can help health care professionals manage prescribing of controlled substances by improving adherence monitoring and offering greater protection from drug misuse and diversion.[¶] Doing so may help overcome a major barrier to effective pain relief—health care professionals’ fear of addiction or relapse of previously addicted patients.³⁰

* Split sample: splitting a single urine void into 2 separate bottles labeled A & B; bottle A is tested; bottle B remains sealed and available for testing at the direction of the donor

† 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

‡ Opioid: a more current term that includes opiates and synthetic/semisynthetic agents that exert their effects by binding to highly selective opioid receptors

§ Substance misuse: use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not

¶ Addiction: a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations

¶ Diversion: diverting drugs from their lawful medical purpose

IMPROVING RELIABILITY OF PATIENT-CENTERED CLINICAL TESTING

The clinical value of UDT depends on the health care professional understanding the strength or weakness of a particular test or the laboratory conducting that test. Because of the necessary evolution of testing technologies and methodologies, it is important for clinicians to be aware of testing practices in general and to dialogue with their testing laboratory personnel (eg, toxicologist, laboratory director) or technical support from the manufacturer of POC devices to be aware of changes that have been made that might materially alter the interpretation of results.^{1,4,32} Many important differences exist between and within laboratories and manufactured POC UDT: for example, the drugs included in the test menu for the immunoassay drug panels, cross-reactivity patterns, cutoff concentrations, and drug interferences.⁹ Correct interpretation of test results requires knowledge and understanding of these variables. In addition, the clinician must 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 medications, or their metabolites, may complicate the accurate interpretation of the results obtained.^{33,34}

Clinicians should advise the testing laboratory if the presence of any particular substance or group of substances is suspected or expected.⁴ When specifically looking for the presence of a prescribed medication, it is advisable to determine with the laboratory in advance if, in fact, it can detect that particular substance, and if so, how the test should be ordered; for example:

1. The initial and confirmatory testing levels for opiates in federal testing were raised from 300 ng/mL to 2000 ng/mL in order to reduce the identification of most individuals who ingest foodstuffs that contain poppy seeds.*⁸ In the clinical setting it is important that 300 ng/mL or less be used for initial screening of opiates. Confirmation testing for opioids when monitoring patients' adherence to a treatment plan should be at the laboratory's limit of detection[†] (LOD). Health care professionals ordering the test should clarify these limits with the testing laboratory and determine whether or not it has the capability to detect substances below the federal cutoff level. If a laboratory does not have established protocols to perform LOD testing, it may not be able to meet such a request—however, a growing number of laboratories are establishing testing menus specifically for use in the pain management setting and this should be considered when selecting a laboratory.
2. The semisynthetic 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. The synthetic opioids, such as fentanyl, meperidine, and methadone, will not be detected by current opiate class immunoassays.

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. These capabilities will also be found in any laboratory that is certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) for federal UDT. However, SAMHSA certification is limited only to the SAMHSA profile and does not cover other drug profiles and tests offered by the laboratory. A call to the laboratory director or toxicologist will help determine that laboratory's analytical capabilities and to clarify one's testing needs, especially around reporting positive results down to the LOD.

WHY TO TEST

The rationale for performing UDT 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, to encourage or reinforce healthy behavioral change, or as a requirement of continued treatment.^{25,33} Frequency of testing should be determined by clinical judgment based on a proper assessment and evaluation of the patient.²⁹ If the patient is displaying aberrant behavior, testing frequency should be sufficient to document patient adherence to the treatment plan.

UDT is commonly included in a written or oral treatment agreement that outlines both the patient's and the health care professional's rights and responsibilities.³⁵⁻³⁸ Such an agreement, which describes a clearly understood and well-defined description of treatment boundaries (eg, pill counts, a random urine specimen for testing when requested), should be in place when treating any patient with a chronic illness, including chronic pain. The treatment agreement should be readable, reasonable, and flexible.³⁹ The fact that the patient and health care professional have agreed to these tests suggests a positive therapeutic alliance.

Advocate for Patients

Health care professionals can use UDT as an objective tool to assist in advocating for patients with family, workplace, and contested situations. UDT is only 1 of the several elements necessary to assess patient adherence to the agreed-upon treatment plan.²⁵ Examples of situations in which UDT may be used as a tool for patient advocacy include social security disability, workers' compensation, and divorce/child custody cases. UDT used with accurate record-keeping and due care can complement other methods used by health care professionals to advocate for patients in such situations.

Identify Use of Illicit or Nonprescribed Licit Drugs

UDT can aid the health care professional in detecting misuse or abuse of illicit or nonprescribed 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

*The following cutoffs 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 >1000 ng/mL without codeine (consistent with morphine use)

†Limit of detection: lowest amount of drug that a laboratory can reliably identify in a specimen; the limit of detection varies depending on the methodology and the laboratory

Table 3. The ten steps of Universal Precautions

1. Make a diagnosis with appropriate differential and a plan for further evaluation and investigation of underlying conditions to try to address the medical condition that is responsible for the pain
2. Psychologic assessment, including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Pre-/post-treatment assessment of pain level and function
6. Appropriate trial of opioid therapy +/- adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the “Four As” of pain medicine^a
 - **A**nalgesia, **A**ctivity, **A**dverse reactions, and **A** aberrant behavior
9. Periodically review management of the underlying condition that is responsible for the pain, the pain diagnosis and comorbid conditions relating to the underlying condition, and the treatment of pain and comorbid disorders
10. Documentation of medical management and of pain management according to state guidelines and requirements for safe prescribing

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

Gourlay DL, Heit HA. *Pain Med.* 2009;10(suppl 2):S115-S123.

^aPassik SD, et al. *Clin Ther.* 2004;26:552-561.

controlled substances (eg, limited dispensing, increased frequency of appointments, pill counts, referral to or consultation with an addiction specialist and/or other mental health care specialist).^{24,24-26} 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.²⁴

A “Universal Precautions”^{*} 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 3).^{24,40} In addition, there is a multiplicity of screening tools that can be used to assist clinicians in assessing patients;²⁶ a review describing the benefits and limitations of several was published by Passik and colleagues in the journal *Pain Medicine*.⁴¹ These tools can help to determine which opioid-treated patients are at increased risk for opioid-related aberrant behavior, and may be used to trigger initial and subsequent drug testing, although their use does not rule out the need for UDT.

Suspected Diversion

Diversion is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale or distribution.²⁷ When determining whether a patient is taking the medications prescribed or to decrease the risk of diversion, it is essential to know the characteristics of the testing procedures, because many drugs are not routinely or reliably detected by all UDT. Also be aware of the ranges and reporting cutoff concentrations that a particular laboratory

uses. The therapeutic doses of some agents might fall below the LOD of UDT designed to deter drug misuse; even misuse of substantial quantities of some drugs may not be detected.

An inappropriately negative UDT result may indicate drug diversion, but it also may occur secondary to maladaptive drug-taking behavior, such as bingeing that may lead to running out early of the prescribed controlled substance.²⁵ This needs to be addressed in a therapeutic context.^{25,29} One should always discuss unexpected results with the patient to determine the “motive” behind the behavior.⁴⁰ A negative urine for a prescribed drug should not be interpreted as definitive evidence of criminal behavior, such as diversion.

WHOM TO TEST

Although there are no pathognomonic signs of addiction/misuse or diversion, the clinical presentations in the following section may be indications for closer monitoring, including increased frequency of UDT and tightening of treatment boundaries. One study among chronic pain patients receiving long-term opioid therapy found that reliance on aberrant behavior alone to trigger 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.^{42,43} Because the validity of drug users’ self-reported substance use is variable, using UDT in addition to self-report, monitoring of behavior, and other clinical tools may provide a more complete diagnostic picture.^{6,25,32,42-45} Likewise, the appearance, ethnicity, language, or culture of a patient is not a reliable indicator of aberrant drug-related behavior; a consistent protocol of performing UDT on all patients receiving or being considered for prescription of controlled substances can help to validate and destigmatize patients. A large study that characterized the drug disposition patterns in 10,922 urine specimens collected from a large population of pain patients found that the frequency of illicit drug use (cannabis, cocaine, ecstasy) was 11.8%.⁴⁶

New Patients Already Receiving a Controlled Substance

In addition to history, physical examination, contacting past health care professionals, requesting past medical records, and querying state PMPs, performing 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 UDT at the initial evaluation can increase both health care professional and patient acceptance of this useful test. When health care professionals introduce UDT 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 thorough evaluation to confirm their presenting condition, or who are reluctant to undergo diagnostic tests, including UDT, are not candidates for therapy with a controlled substance. UDT may still be useful in diagnosing an underlying addictive disorder, even if the decision is made not to prescribe a controlled substance, because an untreated substance-use

^{*}Universal Precautions: recommendations to guide patient assessment, management, and referral to improve patient care, reduce stigma, and contain risk

disorder can adversely affect so many areas of a patient's life, including mood, sleep, and function. Such patients may also be unwilling to give permission for clinicians to obtain past medical records or to communicate with past health care professionals. There are situations in which clinicians may need to make short-term prescribing decisions with limited information; however, clinicians are not required to prescribe “on-demand” for a patient, and they should only prescribe controlled substances after they have appropriately assessed and evaluated the clinical situation.⁴⁰ In the authors' opinion, prescribing controlled substances to patients who are “philosophically opposed” to UDT is relatively contraindicated.³⁹

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, a claim of allergy to all but 1 specific drug with high misuse potential. Unwillingness to try other treatment options with no medical justification is also suspicious and merits further investigation, such as contacting past providers, obtaining old medical records, or querying state PMPs. However, due to pharmacogenetic variability in the type, amount, and duration of metabolites formed—all of which will be affected by interindividual differences in metabolism—an individual's analgesic response to a particular drug may be affected.⁴⁷ In some cases, patients have gone through several regimens to get to one that works well for them and they can sometimes legitimately be reluctant to make changes. As a general rule, however, a prescriber would be wise to avoid prescribing medications that a patient has previously used inappropriately, even if the patient claims that these are the only agents that work.

Patients Who Display Aberrant Behavior

Patients who display problematic drug-related behavior often *repeatedly* want appointments toward the end of office hours or at the end of the week, telephone or arrive after office hours or when they know that their primary health care professional is not available, and may insist on being seen immediately because they are late (for their flight, meeting, child's soccer game, etc).⁴⁸ Aberrant drug-related behaviors that suggest substance misuse or addiction include repeated episodes of prescription loss, or running out of medications prematurely with urgent calls for early refills without following procedures specified in their treatment agreements, seeking out pain medications from multiple doctors without sanction, resistance to changes in therapy, multiple unsanctioned dose escalations or other nonadherence to therapy despite repeated warnings, and concurrent misuse of alcohol, prescription medications, or illicit drugs.^{44,48-50} Often, however, it may be easier to identify aberrant behaviors than the causes or motives behind them.⁵¹ Patients who are not addicted to, misusing, or diverting drugs may display behaviors that appear similar; for example, patients whose pain is undertreated may sometimes display desperate behaviors reminiscent of what one might expect from someone who is addicted. This circumstance is known as pseudoaddiction.^{*50,52} Although no 1 aberrant behavior is pathognomonic of misuse or addiction, such behavior should never be ignored because the diagnosis of addiction is often made prospectively over time. Pseudoaddiction, however, is a diagnosis often made retrospectively—for example, previously aberrant behavior that normalized as a result of aggressive and rational treatment of poorly controlled pain.⁵¹

Patients in Recovery

Patients who have struggled with substance-use disorders are often reluctant to accept even rational pharmacotherapy for pain management. In these cases, routine UDT can provide both reassurance and objective evidence to the treatment team, the patient, and the patient's family of appropriate attention to the increased risks in this patient population. While pharmacologic treatment in these patients is never without risk, that risk can and should be managed.³⁹ An appropriate trial of opioid therapy, generally with adjunctive medication, may be warranted in moderate to severe pain—although opioids should not routinely be thought of as treatment of first choice, they must also not be considered as agents of last resort.³⁹ Implementing monitoring strategies, including UDT, becomes especially important when managing patients who have substance-use histories.³⁹

WHEN TO TEST

When Meeting a Patient for the First Time

Substance-use disorders are not uncommon in the population (they may be more or less common in your practice depending on your demographics), so UDT should be considered a normative part of primary care.²⁹ UDT should be considered as a part of the evaluation of any new patient who is taking controlled substances.

When Starting 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.⁵³ There is no evidence in the literature that rational pharmacotherapy for the treatment of any medical condition ultimately leads to a substance-use disorder; 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.⁵³ This should include a detailed history, but may also include UDT to determine if the patient is taking or has recently taken illicit and/or licit but unprescribed substances.⁵³

A history of substance misuse does not preclude appropriate treatment with any medication, including a controlled substance, but it does increase risk.^{24,26} When indicated (eg, opioid analgesia to relieve pain), it requires a treatment plan with firmly defined boundaries.^{24,26} Clinically, a patient in recovery from the disease of addiction can be cautiously managed by setting careful and strict boundaries, which include random UDT, a treatment agreement, and referral to, or comanagement with, a recovery program[†] or expert in the management of such patients.^{26,35,39} A patient with active addictive disease must start a program for recovery to increase the success of the treatment of his or her pain syndrome before long-term prescribing of controlled substances can be contemplated. Chronic pain problems cannot be solved in the face of active, untreated addiction.⁴⁰

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 or active substance-use disorders, so long as the documented

*Pseudoaddiction: an 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

reason for the treatment is not for the maintenance or detoxification of a concurrent substance-use disorder.¹⁴ A summary of federal regulations for prescribing a controlled substance can be found on the American Society of Addiction Medicine Web site (www.asam.org/pain.html).⁵⁴ It must be emphasized that the controlled substance is prescribed to treat the primary pain disorder, not for maintenance or detoxification of a concurrent substance-use disorder. The records must reflect a clear evaluation of the presenting complaint, the treatment plan, appropriate follow-up of the pain syndrome, and a clear indication for the medical use of opioid therapy.

When Making Major Changes in Treatment

Modification of therapy, particularly dose increase, should depend on the evaluation of progress toward stated treatment objectives—decreased pain and increased function—while monitoring for side effects and aberrant behaviors. If treatment objectives are not being achieved despite medication adjustments, 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).^{35,38} Unexpected positive or negative UDT results, which are confirmed through a discussion with the laboratory and that are not consistent with history gathered from the patient, 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.^{35,38,53}

INTERPRETATION OF UDT RESULTS

UDT in clinical practice, like any other medical test, should be performed to improve patient care.⁴⁰ 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 and over- or under-diagnosis of substance misuse or addiction. Health care professionals should use UDT results in conjunction with other clinical information. Consultation with an individual knowledgeable in UDT interpretation (eg, laboratory director or toxicologist) is strongly encouraged, especially when unexpected test results are obtained. The testing laboratory or POC device manufacturer should provide readily accessible consultation and results interpretation.^{15,32}

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, 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 false-negative results can occur, so it is imperative to interpret UDT results carefully.³³ In addition, testing technology is constantly evolving and varies by manufacturer, so false-positive or false-negative results today may not be relevant in the future.

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.

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 compound.⁹ 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, presence of

cocaine (detected only with very recent use because of a short half-life) or benzoylecgonine is highly predictive of cocaine use.³

- 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 11 for more details).
- Immunoassay testing for opiates is very responsive for morphine and codeine, but does not distinguish which is present. However, it shows a lower sensitivity for semisynthetic/synthetic opioids, and so even large concentrations in the urine may not be reliably detected by the opiate immunoassay (see pages 12-13 for more details).^{9,14,55,56} A negative result does not exclude use of these opioids, but the ability of opiate immunoassays to detect semisynthetic/synthetic opioids varies among assays because of differing cross-reactivity patterns. Specific immunoassay tests for some semisynthetic/synthetic opioids may be available (eg, oxycodone, methadone/EDDP).

Therefore, for clinical purposes, the cocaine assay would be very reliable, while the amphetamine assay would be unreliable in predicting use of the drug, and the opiate assay would be unreliable in predicting use of semisynthetic/synthetic opioids. Fortunately, GC/MS or LC/MS analysis directed toward a particular molecule on the same urine specimen will normally detect these semisynthetic and synthetic opioids—it is important to contact the laboratory when looking for a specific substance to ensure that the correct test/profile is used.

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.^{57,58} Quinolones are not misidentified as opiates by GC/MS or LC/MS. There have also been cases of false-positive fentanyl results with some immunoassays for patients who are taking the antidepressant trazodone,⁵⁹ and the antidepressant venlafaxine can cause false-positive PCP results with some immunoassays.^{60,61} Examples of other agents that can cause false-positive immunoassay results are shown in **Table 5**. Interferences from some of the drugs listed have been eliminated by some manufacturers, and other interferences are expected to arise as tests are modified and new drugs come to market.

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.¹⁵ Long-term use of lipid-soluble drugs, such as marijuana, diazepam, or ketamine, 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.¹⁵ There is currently no scientifically validated relationship between the concentrations reported in the urine and the doses taken of prescribed drugs.^{32,47,70,71}

Any unexpected positive result for drugs of misuse may indicate a substance-use disorder 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.²⁴ Although the substance-use disorder does not diminish the patient's complaint of pain, it does complicate the management of it.

Table 5. Examples of cross-reacting compounds for certain immunoassays

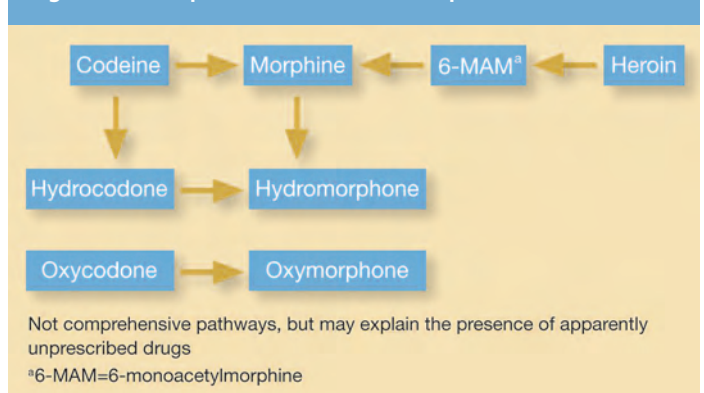
Interfering drug	Immunoassay affected*
Quinolone antibiotics (eg, levofloxacin, ofloxacin) ^{57,58}	Opiates
Antidepressant trazodone ⁵⁹	Fentanyl
Antidepressant venlafaxine ⁶⁰⁻⁶²	Phencyclidine
Atypical antipsychotic quetiapine ⁶³	Methadone
Antiretroviral efavirenz ⁶⁴	THC
Diet pills (eg, clobenzorex, fenproporex) ^{65,66}	Amphetamine
Promethazine (for allergies, agitation, nausea, vomiting) ⁶⁷	Amphetamine
<i>l</i> -methamphetamine (over-the-counter nasal inhaler) ^{65,66}	Amphetamine
Dextromethorphan ⁶⁸	Phencyclidine
Proton pump inhibitors (such as pantoprazole) ⁶⁹	THC

*Only some immunoassays are affected

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.³³ However, a morphine-positive UDT may also result from codeine and from morphine in foodstuffs (eg, poppy seeds in some breads/confectionery).^{8,15,32,72} A specimen that tests positive for morphine with the presence of 6-monoacetylmorphine (6-MAM), a heroin metabolite, is—given our current level of understanding—definitive proof of recent heroin use (**Figure 1**).⁸ 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 UDT.^{8,8,16,73} When heroin use is suspected or reasonable to consider in your area, the laboratory should be questioned regarding under what conditions testing for 6-MAM would be conducted. Since 6-MAM spontaneously degrades to morphine, suspected 6-MAM positive specimens should be frozen to preserve them for retesting, if necessary.

Figure 1. Examples of metabolism of opioids



True-Positive Results With a Medical Explanation

In certain cases, a patient may have a positive UDT result because of medication prescribed by another health care professional, use of OTC products, or consumption of certain foodstuffs that result in a positive screen.⁸ Health care professionals should maintain a list of all prescription and OTC products that a patient is taking while being prescribed controlled substances, and should require patients to notify them prior to adding any new medication. Documenting these agents prior to performing UDT will assist in interpreting both true-positive and false-positive results.

Several examples of true-positive results with a medical explanation are listed below.

Opioid metabolism: (See Figure 1)

- Codeine is metabolized to morphine, so both substances may occur in urine following codeine use:^{8,32,33}
 - A prescription for codeine may explain the presence of both drugs in 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 (7% of the Caucasian population) lack the necessary activity of the cytochrome P450 (CYP) 2D6 enzymatic pathway to convert codeine to morphine.⁷⁴
 - Metabolism of codeine would not result in the presence of hydromorphone.
- Morphine may be metabolized to produce small amounts (generally <10%) of hydromorphone.^{34,75-80}
- Hydrocodone may be metabolized to small quantities of hydromorphone.^{81,82}
- Metabolism of codeine may produce small quantities of hydrocodone.⁸³
- Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone.^{3,84} If the urine of a patient prescribed oxycodone tests positive for oxymorphone, a quantitative analysis should confirm—in the majority of cases—that the relative concentration of oxycodone is greater than oxymorphone.³ Test results for patients prescribed oxymorphone are easier to interpret because oxymorphone does not produce any metabolites that can be mistaken for another opioid (although oxymorphone tablets may contain up to 1% oxycodone as a manufacturing byproduct, which should generally not be detectable with UDT).³

Cocaine: Cocaine is a topical anesthetic clinically used in certain trauma, dental, ophthalmologic, and otolaryngologic procedures.⁸ 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 health care professional must order its use, which can be checked through medical records or by contacting the treating health care professional. There is no structural similarity between other

topical anesthetics that end in “caine” (eg, prilocaine, lidocaine) and cocaine or benzoylecgonine; therefore, cross-reaction does not occur.⁸ A positive UDT result for the cocaine metabolite, in the absence of a medical explanation, should be interpreted as due to deliberate use.³

Amphetamine/Methamphetamine: Clinical interpretation of positive amphetamine and methamphetamine results can be challenging because of the structural similarities to many prescription and OTC products, including diet agents, decongestants, and selegiline used in the treatment of Parkinsons 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 is not sufficient to distinguish methamphetamine use from use of OTC products. Methamphetamine exists as 2 isomers that are designated *d*- and *l*-.⁸ 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. In a case of disputed amphetamine or methamphetamine misuse, stereospecific chromatography may be used in addition to GC/MS.

For example, the OTC Vicks® Inhaler marketed in the United States contains *l*-desoxyephedrine (*l*-methamphetamine).⁸ Patients whose management includes UDT 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.³³ These results may also occur because of cross-reactivity with other compounds found in the urine. GC/MS and LC/MS, or similar technologies, are not influenced by cross-reacting compounds.^{8,15,57} 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 the health care professional.

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.^{15,33} 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.

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

Health care professionals should be aware of the time taken for drugs to be eliminated from the body because 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.³³ This may occur through laboratory or clerical error or 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 or 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 and well characterized.⁸ If tampering is suspected, urine temperature and pH should be checked, and ordering of an “adulteration panel”^{*} from the laboratory should be considered.⁸

CAVEATS TO INTERPRETATION

Drug Metabolites

In general, the concentration of the parent drug in urine exceeds that of its metabolite(s). In certain cases, UDT may detect traces of unexplained opioids (see Figure 1). For example, a patient who is prescribed codeine may show trace quantities of hydrocodone that may not represent hydrocodone use.⁸³ Detection of minor amounts of hydrocodone in urine containing a high concentration of codeine should not be interpreted as evidence of hydrocodone use. In the case of a patient who is prescribed hydrocodone, quantities of hydromorphone may be detected because of hydrocodone metabolism.^{81,82} However, the detection of trace amounts of a potential metabolite in the absence of its parent may be a timing of administration issue rather than coadministration of a 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

UDT 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 (Table 6).

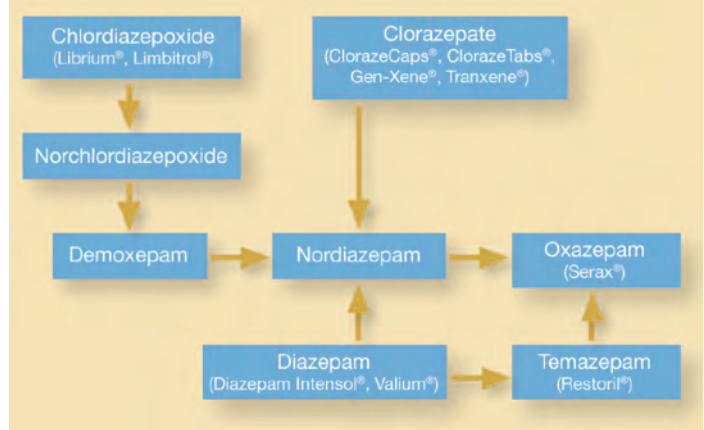
Pitfalls of Monitoring Prescribed Medications

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 reasons may lead to not finding a prescribed medication in the patient’s urine (See Table 6). 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 dialogue with the patient to clarify this result.

Table 6. Reasons why a particular drug or medication is not detected in a patient’s urine sample

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

Figure 2. Some examples of benzodiazepine pathways of metabolism



Another limitation of UDT is that the presence of a prescribed drug cannot distinguish whether the patient has been taking the drug as directed or uses only a portion of the prescribed medication (potentially selling the rest). Therefore, it is important that UDT is interpreted within the whole clinical context of the patient, including other methods of assessing adherence (eg, pill counts, PMPs).

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 7), unless an immunoassay directed toward that particular molecule is used.⁸ It is possible that some semisynthetic opioids, even at high concentrations, will be inconsistently detected by the immunoassay tests because of incomplete cross-reactivity.

Synthetic Opioids: Only immunoassays specifically directed toward the molecule will detect synthetic opioids, such as methadone or fentanyl.

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 UDT.⁸⁵ Most respondents were unaware that oxycodone is not detected by most opiate immunoassays.⁸⁵ In another study, only 23% of family physicians receiving an abnormal or unexpected UDT result indicated that they would consult with the laboratory about the possible meaning of the result.³¹

^{*}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

Table 7. Source of opioid analgesics

Natural (extracted from opium)	Semisynthetic (derived from opium extracts)	Synthetic (completely man-made)
• Codeine	• Hydrocodone	• Meperidine
• Morphine	• Oxycodone	• Fentanyl family
• Thebaine	• Hydromorphone	• Propoxyphene
	• Oxymorphone	• Methadone
	• Buprenorphine	• Tapentadol

Benzodiazepines: Variability in immunoassay cross-reactivity also applies to benzodiazepines. While many benzodiazepines are generally detected by immunoassay, not all benzodiazepines are equally detectable by all reagents. Clinicians should carefully interpret the presence or absence of the benzodiazepine class when assessing treatment adherence. They should be aware of the metabolic pathways of different benzodiazepines in order to correctly interpret results (Figure 2).

Concentration Effects: It is important to know the threshold concentrations that your laboratory uses when interpreting a report of “no drug present.”^{1,33} A drug may be present in the sample, but below the laboratory’s reporting 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.

Amount of Drug Taken: At this time, there is no scientifically validated relationship between the amount of drug taken and urine drug concentration. Therefore, UDT cannot indicate the amount of drug taken, when the last dose was administered, or the source of that drug.^{4,32} Recently, some laboratories have offered technology to calculate a normalized value based on the patient’s height and weight and the specimen’s pH and specific gravity to extrapolate the 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 of the prescribed drug. Software and laboratory products have not yet been fully validated scientifically and peer reviewed in the medical literature. Interpreting UDT beyond the current scientific knowledge may put health care professionals and patients at medical and/or legal risk.^{47,71} Other laboratories utilize normalized urine concentrations in comparison to statistical outcomes in very large drug-usage populations. Such comparison ranges may provide a measure of adherence with drug use, and ranges of doses (ie, in range, low, or high) may be reported. These may be useful to allow the clinician a tool for consultation with a patient.

MYTHS

Passive Inhalation

Passive smoke inhalation does not explain positive marijuana results at typical cutoffs (50 ng/mL).^{8,15} 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

11-nor-delta-9-tetrahydrocannabinol (THC) is the principal active ingredient of smoked marijuana (*Cannabis sativa* L.). THC has been marketed under the trade name Marinol® (dronabinol) for the control of nausea and vomiting in cancer patients receiving chemotherapy and as an appetite stimulant for AIDS patients.⁸⁶ The synthetic cannabinoid nabilone (Cesamet®) is also approved to treat nausea and vomiting associated with cancer chemotherapy in patients who have failed to adequately respond to conventional antiemetics.^{87,88} Another drug currently available in Canada (in clinical trials in the United States) 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, but is also used in clinical practice for other neuropathic pain states and as an adjunctive analgesic in patients with advanced cancer.⁸⁹⁻⁹¹

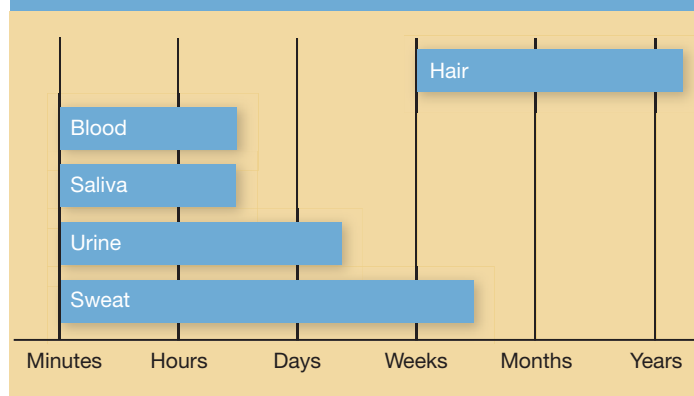
Smoked cannabis, orally administered Marinol®, and buccal Sativex® all produce immunoassay-positive screen results for the THC metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THCA). More specific testing may be able to distinguish the subtle differences between smoked and pharmaceutical THC. However, Cesamet® does not trigger a positive immunoassay screen or a confirmatory GC/MS for THCA because it does not contain THC.⁸⁷ There have been reports of false-positive urine immunoassay tests for cannabinoids in patients receiving proton pump inhibitors, such as pantoprazole (Protonix®).⁶⁹ However, a confirmatory test such as GC/MS or LC/MS rules out this cross-reactivity.

Food 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.^{92,93} However, multiple studies have found that the THC concentrations typical in hemp products are sufficiently low to prevent a positive immunoassay result.^{92,93} There was a recent report by the Centers for Disease Control and Prevention of inadvertent ingestion of marijuana among a group of preschool teachers who experienced nausea, dizziness, headache, and numbness/tingling of fingertips after consumption of brownies purchased from a sidewalk vendor.⁹⁴ Analysis detected cannabinoids in a recovered sample of the brownies and 1 of 2 patients who sought medical attention had a urine sample test positive for THC.⁹⁴

There have been documented cases of cocaine ingestion by drinking tea made from coca leaves.^{8,95} Although such tea may be available for purchase by unknowing consumers, the product—containing cocaine and/or related metabolites—is illegal under the US Drug Enforcement Administration and US Food and Drug Administration regulations. Patients should be advised not to ingest hemp products or coca tea.

Figure 3. Relative detection times of drugs in biologic specimens⁷⁰



ALTERNATIVE TECHNOLOGIES FOR DRUG TESTING: BENEFITS & LIMITATIONS

Drugs can be detected in many other biologic specimens, including hair, oral fluid, blood, sweat, nails, and semen.⁹⁶ Several specimens are available as alternatives to urine for drug testing, including blood, oral fluid, hair, and sweat.^{1,65} This section will briefly compare with urine the pattern of information offered by each specimen regarding drug use over time and particular strengths and weaknesses regarding the type of information that may be obtained, ease of collection, degree of invasiveness, analytical and testing considerations, interpretation of results, and cost.^{5,7,65,96}

The window of drug detection for urine, hair, oral fluid, and sweat are not identical, but the results from each specimen can complement each other (Figure 3).^{65,70,97} Characterization of the disposition of different drug classes in these biologic matrices and the effect of chemical, physiologic, and pharmacologic factors are important for accurate interpretation of results.⁹⁸⁻¹⁰⁰ Some drug classes are more difficult to detect than others for a given type of specimen.^{1,97}

Blood: Blood testing can effectively detect low levels of substances and practically is a better sample for the assessment of an intoxicated patient.¹ However, it is an invasive and expensive procedure with a window of detection that is limited to current drug use, and is not as amenable to rapid screening procedures.⁶⁵

Oral Fluid: Oral fluid testing is increasing in popularity because it overcomes some of the problems of urine, which include accessible collection in almost any location, less embarrassment, observable conditions, and limited invasiveness.^{11,65,98,101-103} Researchers comparing the effectiveness of oral fluid testing with UDT found a similar pattern and frequency of positive drug test results in the general workforce over the same general period.^{65,104}

Oral fluid is composed of saliva, mixed with gingival crevicular fluid, buccal and mucosal transudates, cellular debris, bacteria, and residue of ingested products.⁹⁸ Oral fluid specimens are considered to reflect circulating drug concentrations because salivary glands are highly perfused, allowing rapid transfer of a drug from blood to oral fluid.⁹⁸ Thus drugs are detected earlier in saliva than in urine, but for shorter time periods.¹¹ Oral fluid is generally useful for detecting drugs in the range of less than 1 hour up to 4 hours, but some drugs can be detected for up to 24 hours.^{65,97} It is amenable particularly to post-accident testing.

Collection procedures are not standardized and can affect drug concentrations.¹¹ Specimens are collected by having the patient expectorate into a container, or by using a commercially available collection device. Absorption of the drug to the material of a collection device also introduces issues of drug recovery compared with neat oral fluid.^{11,98,105} The sample volume of saliva necessary for laboratory testing may be difficult to obtain, and considerably lower drug concentrations compared with urine present an analytical challenge.¹¹

Oral fluid as a test matrix shows promise for detection of recent drug use, and a significant body of scientific literature documents aspects such as drug disposition and detection times.^{11,98} It has not yet been determined, however, whether adulterants exist that can be safely placed in the mouth

to produce false-negative results, and evidence on interferences of common compounds present in the mouth, residual drug in the oral cavity, and other issues of manipulation are currently lacking.^{11,98,105}

Hair: The disposition of drugs in the body includes incorporation into growing hair.¹⁰⁶ Hair may be useful to objectively document past drug use, but it is usually inefficient for clinical testing.^{65,106} Testing hair can extend the window of detection for a drug to weeks, months, or even years depending on the length of the hair tested.^{65,97,107} However, dose and time relationships for drugs in hair are not clear—some studies support that segmental hair analysis can provide a chronologic record of drug use, but others have found high variability in such results.^{7,32,96}

Several mechanisms for incorporation of drugs into hair have been proposed.¹⁰⁶ Drugs can diffuse from arterial capillaries near the root into hair matrix cells at the base of hair follicles, and drugs in sweat and sebum on the skin's surface contact hair and contribute to drug incorporation.^{99,106} The ability of hair testing to distinguish drug use from external contamination (eg, drugs in smoke or the environment) remains controversial.^{96,106} Measuring metabolites and washing hair samples can help prevent false-positive results from external contamination.¹⁰⁶

Darkly pigmented hair has a greater capacity to bind a drug than hair that is light or gray, leading to the claim that hair analysis might have a color or racial bias.^{7,32,33,65,96} Other disadvantages of hair analysis to validate drug use include irregular growth, labor-intensive sample preparation, low analyte concentrations, and excessive cost.^{7,33,96} Differences in hairstyle lengths may affect ability to analyze hair specimens, and hair treatments such as bleaching, dyeing, and permanent waves can alter drug concentrations in hair.⁹⁶ However, methods for evading UDT do not affect hair analysis, and collection can be performed under close supervision.¹⁰⁷

Sweat: Sweat could potentially provide a convenient, less invasive collection method and a longer detection window than urine for most drugs.^{99,108} The window of drug detection for a sweat patch is a cumulative measure of drug use from shortly before the patch is applied until it is removed, which may be from several days to weeks.^{65,97,99} Sweat testing may be most useful to deter future drug use in patients participating in substance-use treatment programs, but would not be useful to monitor drug use for pain management.^{65,97,99}

The mechanisms by which drugs are incorporated into sweat are not fully understood.¹⁰⁰ Drugs primarily passively diffuse from blood to the sweat gland, but also dissolve in sweat on the skin's surface after diffusing through the stratum corneum.^{100,108} Sources of drug concentration variability include the site of patch application, intrasubject and intersubject variability in sweat production, loss or dynamic exchange of drug between the patch and skin, and environmental contamination.^{99,100,108} Newer nonocclusive patches use a transparent film that allows oxygen, carbon dioxide, and water vapor to escape. Researchers have demonstrated low acceptability by patients (only half of applied patches were brought back attached to the skin) and a low sensitivity for detecting illicit opioid use (sweat patches detected one-third of illicit opioid-use instances detected by weekly UDT).¹⁰⁸

Alternative Specimens Summary: New diagnostic tests are developed to improve clinical utility, accuracy, convenience for the patient and/or clinician, and to decrease expense and turnaround time.¹⁰¹ Different biologic matrices have different cutoff concentrations for various drugs, but criteria for specimen validity evaluation for hair, oral fluid, and sweat-patch specimens have yet to be defined.⁹⁷ At present, much

of the available knowledge on drug disposition in biologic matrices has been generated from single- or multiple-dosing studies, but information is limited in chronic users.⁹⁸ Ethical issues exist in the study of many licit and illicit drugs that preclude their study under conditions that simulate “real-world use”, and relevant information may never be available.⁹⁸ Oral fluid is promising and may be a valuable complement to UDT in clinical pain management settings.¹⁰⁸

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 following use. Ethyl glucuronide (EtG) is a minor metabolite of alcohol formed by conjugation.¹⁰⁹ 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, although there is wide inter-individual variability).¹¹⁰⁻¹¹² Thus, EtG becomes a sensitive and specific marker to detect alcohol use or exposure, 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, “nonalcoholic” 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.¹⁰⁹ 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 to understand potential causes of false-positive or false-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.¹¹³ Significantly elevated EtG concentrations can result from hand washing with common hand disinfectants (eg, Purell, 62% ethyl alcohol).¹¹⁴ EtG test results should be used as a diagnostic aid in the total management of the patient. Health care professionals are cautioned that alcohol is present in many non-beverage products that can produce a positive result, and a full evaluation of all positive results needs to be made.

The US Department of Health and Human Services has issued a boxed warning which states:¹¹⁵

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

UDT can be an effective tool for health care professionals in the assessment and ongoing management of patients who:

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

Because substance-use disorders are common, UDT should be considered a core tool in primary care. The clinician can use a discordant UDT result to motivate patient behavior change. However, testing without an appropriate strategy for interpreting results can do harm. A working relationship with the testing laboratory or test kit provider is essential to accurately interpret UDT results. Most importantly, a health care professional should strive for a relationship of mutual honesty and trust with the patient when using UDT in his or her clinical practice. Therefore, the use of UDT should be consensual, be designed to help patients, and assist health care professionals to advocate for the health and well-being of their patients.

PRACTICAL STRATEGIES

- Select a testing laboratory or POC device supplier
- For limited testing, establish a routine UDT immunoassay panel:
 - Recommended drugs/drug classes to screen for are:
 - Cocaine
 - Methadone
 - Amphetamines (including ecstasy)
 - Marijuana
 - Opiates
 - Benzodiazepines
 - Oxycodone
 - Additional tests may be added as needed
 - Confirmation testing may be added
- For patients prescribed opioids, request LOD testing to increase likelihood of detecting prescribed medications:
 - GC/MS or LC/MS identification
 - Many laboratories have a specific chromatographic pain management panel that may include the following:

<i>Amphetamines</i>	<i>Barbiturates</i>	<i>Benzodiazepines</i>	<i>Opioids</i>	<i>Miscellaneous</i>
Amphetamine	Amobarbital	Alprazolam	Codeine	Carisoprodol
Methamphetamine	Butabarbital	Chlordiazepoxide	Dihydrocodeine	Meprobamate
Phentermine	Butalbital	Clonazepam	Fentanyl	<i>Illicit Drugs</i>
	Pentobarbital	Clorazepate	Hydrocodone	Cocaine/Crack
	Phenobarbital	Diazepam	Hydromorphone	Heroin
	Secobarbital	Flurazepam	Meperidine	MDA
		Lorazepam	Methadone	MDEA
		Oxazepam	Morphine	MDMA
		Temazepam	Oxycodone	Marijuana
			Oxymorphone	Paramethoxyamphetamine
			Propoxyphene	

- 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” from your laboratory
 - Submit the suspected sample as well as a fresh sample
- 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 opportunities
 - Use results to strengthen the health care professional-patient relationship and to support positive behavior change
 - Chart results and interpretation

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GLOSSARY

Addiction: A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations

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

Diversion: Diverting drugs from their lawful medical purpose

GC/MS: 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

LC/MS: Liquid chromatography is used to separate the different components in a specimen, and mass spectrometry is used to specifically identify the components of the specimen

Limit of detection: lowest amount of drug that a laboratory can reliably identify in a specimen; the limit of detection varies depending on the methodology and the laboratory

Opiate: 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

POC: On-site or point-of-care testing using commercial devices without the need for instrumentation

Pseudoaddiction: An 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 2 separate bottles labeled A and B; bottle A is tested; bottle B remains sealed and available for testing at the direction of the donor

Substance misuse: Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not

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

ABBREVIATIONS

6-MAM	6-monoacetylmorphine
CNS	central nervous system
CYP	cytochrome P450
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EtG	ethyl glucuronide
GC/MS	gas chromatography/mass spectrometry
LC/MS	liquid chromatography/mass spectrometry
LOD	limit of detection
MDA	3,4-methylenedioxyamphetamine
MDEA	3,4-methylenedioxyethylamphetamine
MDMA	3,4-methylenedioxymethamphetamine
OTC	over-the-counter
PCP	phencyclidine
PMP	prescription monitoring program
POC	point-of-care
SAMHSA	Substance Abuse and Mental Health Services Administration
THC	11-nor-delta-9-tetrahydrocannabinol
THCA	11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid
UDT	urine drug testing

