Urine Drug Testing in Clinical Practice

The Art and Science of Patient Care

EDITION 5

Target Audience: Physicians who treat patients with chronic pain
There are no prerequisites

Release date: June 15, 2012 ■ ***Expiration date:*** June 15, 2014

Estimated time to complete this CME activity: 2.0 hours

Fee: No fee

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Presented by the Johns Hopkins University School of Medicine

Supported by educational grants from Purdue Pharma L.P.
and Quest Diagnostics Incorporated

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NEEDS STATEMENT

The purpose of this continuing medical education (CME) monograph is to provide clinicians with an overview and understanding of the benefits and limitations of urine drug testing (UDT) in the management of their patients with chronic pain. Opioids are controlled substances that can be a useful component for managing many patients with chronic pain, but they also have the potential for misuse or abuse. UDT, when used appropriately, can be a valuable tool to help physicians manage their patients responsibly.

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 will demonstrate the ability to:

1. Describe the clinical guidelines on appropriate use of UDT in the management plan for patients with chronic pain
2. Differentiate between the use of UDT for monitoring adherence to therapy and for detection of aberrant drug-related behaviors
3. Formulate practice strategies to determine the appropriate test to order and accurately interpret UDT results
4. Create a practice plan to maximize clinical utility of UDT results by correctly interpreting results, charting the interpretation, and consultation with a toxicologist/laboratory director when necessary

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Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

CONTENTS

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. It is designed to assist clinicians to use a clear testing strategy to pursue UDT further in their practices as part of a balanced approach to risk management and optimal medical care when prescribing controlled substances.

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 (eg, preemployment screening and workplace testing). Forensic UDT generally assumes that the majority of donors will be negative for a limited panel of specified substances that may have misuse liability. In contrast, in patient-centered UDT, the majority of donors are in fact positive for a broader range of drug(s) of interest since these are often prescribed for legitimate medical purposes. This adds 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 2 main types of UDT—which are often used in combination—are:

1. Immunoassay drug testing: either laboratory based or at point-of-care* (POC)
2. Laboratory-based specific drug identification†: eg, gas chromatography/mass spectrometry‡ (GC/MS) or liquid chromatography/mass spectrometry§ (LC/MS)

UDT typically detects the parent drug and/or its metabolite(s) and, therefore, demonstrates recent use of prescription medications, unprescribed drugs, 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 16-17.[5;7]

*Point-of-care testing (POC): on-site testing designed to be used where the sample is collected using either instrumented or noninstrumented commercial devices

†In forensic models of testing, the terms "confirmation" or "confirmatory testing" are used, but clinical testing with combination technologies like GC/MS is more about "specific drug identification." Although these terms are often used interchangeably, clinical drug testing is often more about identifying the specific agent causing the positive result, rather than "confirming by a second scientific method" an analyte that has been detected, for the purposes of use in a forensic setting.

‡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

Clinical practice guidelines for the management of chronic pain—published by the American Pain Society (APS)/American Academy of Pain Medicine (AAPM) and the Department of Veterans Affairs/Department of Defense (VA/DoD)—include a provision for UDT.[8;9] However, neither provides instruction for how UDT should be performed rationally in clinical practice.[8;9]

This monograph will help clinicians in deciding when to order UDT and the type of UDT to order for an individual patient, and how to interpret results in order to use UDT as a clinical tool to improve patient care, including strategies for risk management. However, overinterpreting the results, not understanding the limitations of testing, or using UDT results in isolation could lead to clinical decisions that are detrimental to both the provider and the patient, such as adversely altering or even terminating patient care. The monograph will also provide advice for interacting with the testing laboratory or device manufacturer (at the outset of testing and thereafter, as necessary) to ensure that the tests are being used optimally to enhance clinical care.

A summary of "practical strategies" can be found on the inside back cover for clinicians to refer to.

URINE DRUG TESTING METHODS

For most clinical and forensic applications, initial testing continues to be 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. However, with the emergence of laboratories focusing on pain management, some are eliminating initial immunoassay testing in favor of panels utilizing more definitive GC/MS or LC/MS testing. The UDT method chosen should be a function of the question that needs to be answered. It is important that clinicians understand the methods for UDT in order to correctly interpret results.[8]

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.[10] 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 the 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 would be reported as negative, while 51 ng/mL would be reported as positive, although these results are, for scientific purposes, identical). Immunoassays are also subject to cross-reactivity;[10] ie, substances with similar, and sometimes dissimilar, chemical compositions may cause a test to appear positive for the target drug (see pages 11-12 for more details). Samples that test positive by immunoassay for classes of drug need to be tested in the laboratory by a more definitive method if specific identification of the drug is required (such as contested results).

Point-of-Care Testing

A number of single-use noninstrumented immunoassay devices and, more recently, instrumented devices are commercially available for POC testing of some individual or common classes of drugs. POC testing activities are performed outside of the physical facilities of the clinical laboratory. POC testing is intended to provide results more rapidly than a testing laboratory, and so may expedite treatment decisions and provide convenience for the patient and provider,

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

sometimes at the expense of accuracy and reliability.[11;12-15] POC testing may be particularly useful to quickly evaluate new patients for abuse of illegal drugs. Many of these test systems are waived under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and can be performed without routine regulatory oversight under a Certificate of Waiver* from the Centers for Medicare & Medicaid Services.[12;13] Providers who elect to use POC testing need to consider regulatory requirements; safety, physical, and environmental requirements; benefits and costs; staffing; and documentation.[12;16] Before deciding to begin testing or adding a new test to the POC test menu, it is important to weigh the potential benefits and limitations.[12]

Noninstrumented POC devices (eg, urine dipsticks, cups) typically use immunochromatographic methods that produce visually read results.[11;17] These portable tests are typically performed by health care workers whose roles include a variety of nontesting-related duties.[11] Most noninstrumented 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 distinct colored band (negative result) in the test window.[17;18] 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 the antibody from binding the immobilized drug conjugate, so no line forms in the window (positive result)—this is a counterintuitive response. However, some noninstrumented POC devices now operate more logically and produce a colored band for a positive result.

Potential disadvantages include the subjective nature of the noninstrumented devices, lack of automated quality assurance and quality control (eg, the integrity of the test reagents following transportation and storage), data management issues, and cost.[11;15;19;20]

Instrumented POC testing involves benchtop and small floor model immunoassay analyzers that provide enhanced automation, software applications for quality control, and connectivity with health care-information systems and electronic medical records (EMR) systems, so that patient results can be uploaded to their EMR.[13] Instrumented POC testing has some advantages in terms of volumes of tests performed, shorter time frame, and eliminating visual decision making. However, it still suffers from the same shortcomings of cross-reactivity common to both noninstrumented POC testing and laboratory immunoassay testing. Because POC testing devices use the same technology as laboratory immunoassays, if more definitive testing is required to specifically identify the presence of a given drug or its metabolite, more sophisticated tests such as GC/MS or LC/MS should be used.

Although POC tests are designed to be simple to use, they utilize complicated technology and still require proficiency to produce acceptable performance.[11;17;20-22] The operator of POC testing must use good laboratory practice to enable them to produce reliable, clinically useful results.[11] Training of users should include quality issues and recognition of any device limitations.[20] In contrast to testing laboratories, POC devices 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. Because those performing POC tests are not specialists in laboratory testing, and because the tests are frequently performed in settings where a lot of other medical and nonmedical activities compete for attention, managing POC testing is often challenging.[11]

Although performance of POC tests have minimal requirements (simply that of following the manufacturer's recommendations), studies have demonstrated that performance of POC tests often do not adhere to manufacturers' recommendations and variable error rates occur.[14;23] Record keeping of quality control, testing personnel training and competency, and patient test results are crucial—"If it was not documented, it was not done."[11]

LABORATORY-BASED SPECIFIC DRUG IDENTIFICATION

Generally, a more definitive laboratory-based procedure (eg, GC/MS, LC/MS) to identify specific drugs and/or their metabolites is needed in 3 instances: (1) to specifically identify the drug; for example, that morphine is the opiate causing the positive immunoassay response; (2) to identify drugs not otherwise included in other testing methods; and (3) when results are disputed by the patient (ie, 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.[24] 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**).[25;26] Long-term use of lipid-soluble drugs such as marijuana, diazepam, ketamine, or phencyclidine

Table 1. Approximate windows of detection of drugs in urine

Drug	General detection time in urine
Amphetamines	Up to 3 days
THCA (depending on the grade and frequency of marijuana use) – Single use – Chronic use	 – 1 to 3 days – Up to 30 days
Cocaine – BEG after cocaine use	Hours – 2 to 4 days
Opiates (morphine, codeine) – Heroin – 6-MAM	2 to 3 days – 3 to 5 minutes – 25 to 30 minutes
Methadone – EDDP (methadone metabolite)	Up to 3 days – Up to 6 days
Benzodiazepines (depending on specific agent and quantity used)	Days to weeks

6-MAM=6-monoacetylmorphine;
BEG=benzoylecgonine;
EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine;
THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

*The current US Food and Drug Administration (FDA) list of waived tests can be found at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm

Table 2. Normal characteristics of a urine specimen[27-29]	
Temperature within 4 minutes of voiding	90°F to 100°F[a]
pH	4.5 to 8.0[b]
Urinary creatinine	>20 mg/dL
Specific gravity	>1.003

[a]If the sample is of sufficient volume (30 mL or more) and the patient is normothermic
[b]Sample degradation, due to improper storage or prolonged transportation, even in the absence of sample adulteration, can result in sample pH in excess of 8.0.[30]

(PCP) may extend the window of detection to a week or more. Drugs that are rapidly metabolized (ie, have a short half-life), such as cocaine, are mainly detected indirectly by their metabolites, in this case benzoylecgonine (BEG)—identifying cocaine in a urine specimen indicates either very recent use or contamination of the specimen with the parent drug by the donor at the time of collection.

CHARACTERISTICS OF URINE

The characterization of a urine specimen is based on its appearance, temperature, pH, urinary creatinine concentration, and specific gravity (**Table 2**).[10;27-30] Aberrant test results should be discussed with the patient and/or the laboratory, as necessary. 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 volume loading. 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 ability of the patient to produce periodic concentrated specimens reduces the likelihood of any chronic renal pathology causing a dilute specimen.

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 in a separate container and both sent for analysis. Laboratories keep specimens for a variable period of time; check with the laboratory before testing to ensure specimens are available and maintained, should additional testing be required for both negative and positive results.

CURRENT USES OF URINE DRUG TESTING

Though forensic UDT should not be routinely performed by primary care clinicians, it remains 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.[10;29;31] 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:[29]

- 3,4-methylenedioxymethamphetamine (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.[10] In the federal model, the results must be confirmed by a more specific method such as GC/MS or LC/MS.[29] The cost associated with the split sample‡ and chain of custody§ requirements for federally regulated testing are not necessary to incur in clinical practice. **Table 3** shows the most recent federally mandated immunoassay screening and confirmation cutoff concentrations for the "Federal Five."[20] 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 typically too high to be of value in clinical practice. While the entire forensic testing paradigm is of limited use in clinical care, it does set a standard for analytical quality and precision measurement.

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 or commercial driver's license renewal after drug-related revocation or suspension; within the criminal justice system; for insurance or workers' compensation; sports testing; preemployment screening; school children participating in competitive extracurricular activities; and random workplace testing.[4;33;34] Such nonregulated testing may utilize a chain of custody, split samples, and secure storage of non-negative test specimens.[33] 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

*Analyte: any material or chemical substance subjected to analysis
†Opiate: historical term restricted to naturally occurring alkaloids derived from opium (morphine, codeine, thebaine)
‡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 natural "opiates" and synthetic/semisynthetic agents that exert their effects by binding to highly selective μ receptors

Table 3. Initial and confirmatory cutoff concentrations[a] used for federally regulated testing (effective October 1, 2010])[20]

Initial test analyte	Initial test cutoff	Confirmatory test analyte	Confirmatory test cutoff
Marijuana/metabolites	50 ng/mL	THCA	15 ng/mL
Cocaine/metabolites	300 ng/mL	BEG	150 ng/mL
Opiate/metabolites • Codeine/morphine[b] • 6-MAM	2000 ng/mL 10 ng/mL	Codeine Morphine 6-MAM	2000 ng/mL 2000 ng/mL 10 ng/mL
PCP	25 ng/mL	PCP	25 ng/mL
Amphetamines • Amphetamine/methamphetamine[c] • MDMA	500 ng/mL 500 ng/mL	Amphetamine Methamphetamine[d] MDMA MDA MDEA	250 ng/mL 250 ng/mL 250 ng/mL 250 ng/mL 250 ng/mL

THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid; BEG=benzoylecgonine; 6-MAM=6-monoacetylmorphine; PCP=phencyclidine; MDMA=methylenedioxymethamphetamine; MDA=methylenedioxyamphetamine; MDEA=methylenedioxyethylamphetamine

[a]These concentrations used in initial and confirmatory testing are specific to regulated testing and have limited value in clinical testing. It is essential to know the cut-off concentration for reporting a positive result in any test that you order; eg, POC immunoassay opiate testing may be either at 2000 ng/mL or the more clinically useful 300 ng/mL.

[b]Morphine is the target analyte for codeine/morphine testing

[c]Methamphetamine is the target analyte for amphetamine/methamphetamine testing

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

include methadone, buprenorphine, benzodiazepines, oxycodone, and barbiturates, with more being added continually.[3;10]

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) and/or metabolites of interest, since these are often prescribed for legitimate medical purposes.[35] Controversies exist regarding the clinical value of UDT, partly because in the past methods were designed for, or adapted from, forensic or workplace deterrent-based testing for illicit drug use.[1] However, many laboratories now specialize in pain management testing with a panel of analytes that is optimized for clinical use. When used with an appropriate level of understanding, UDT can improve a clinician's ability to manage therapy with prescription drugs (including controlled substances), to assist in the diagnosis of substance misuse* or addiction†, to guide treatment, and to advocate for patients.[1;5;9;35-37] 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 suspected of misusing 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 healthy behavioral change, and to direct appropriate further treatment.[1] Other clinical uses include testing prior to certain medical procedures and testing pregnant women at risk for substance misuse or addiction.[1;38]

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), and to identify drug misuse or addiction prior to starting or during treatment with controlled substances.[8;9;36;39-41] Just as clinicians use hemoglobin A1c to monitor glycemic control 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 and to guide ongoing treatment, especially with agents that have known abuse potential.[39] Testing cannot, however, substitute for diagnostic skills or an ongoing therapeutic alliance with a patient.[25] Overreliance on laboratory testing without good clinical judgment—particularly for contested results—can increase the focus on the test at the expense of a good therapeutic relationship with the patient.[42]

UDT is generally underutilized and, when used, is unfortunately sometimes used inappropriately in clinical practice:

- Eighteen months following the introduction of opioid-dosing guidelines in Washington State in 2007, which included a recommendation for judicious use of random UDT, a survey of primary care physicians found that 20% of respondents were using random UDT always or almost always, 18% often, 32% sometimes, and 30% never or almost never.[43]
- A retrospective review of medical records of 1612 patients in primary care practices receiving opioid analgesics for chronic noncancer pain found that only 8% of providers had utilized UDT.[44]

*Substance misuse: use of a medication 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

‡There is no scientific evidence to support the notion that quantitative UDT provides more information than qualitative UDT with respect to determining patient adherence with specific dosing recommendations

- A 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.[45]
- A survey completed by 49 attendees at the 2008 American Congress of Pain Medicine found that although all respondents reported treating chronic pain patients utilizing opioid therapy, 9 respondents (18%) did not conduct UDT.[46] Only 30% of the pain clinicians had been trained in using UDT.
- In a published survey of primary care physicians, only 7% ordered UDT before prescribing opioids, and only 15% had at least once tested established chronic pain patients already prescribed opioids.[47]

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*.[8;9;40] Doing so may help overcome a major barrier to effective pain relief—health care professionals' fear of addiction or relapse of previously addicted patients.[48] However, while some clinicians may feel more comfortable utilizing UDT in clinical care, it is important that they also recognize the pitfalls and limitations of testing, and seek advice from colleagues to overcome these challenges when ordering tests and interpreting results.[8;9]

IMPROVING RELIABILITY OF PATIENT-CENTERED CLINICAL TESTING

The clinical value of UDT depends on the health care professional understanding the strength and 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;8;49] 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 (which change over time); cutoff concentrations; and drug interferences.[17] 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.[50;51]

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 at what concentrations, 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†.[10;52] In the clinical setting it is important that 300 ng/mL or less be used for initial screening of opiates. Laboratory-based specific drug identification for opioids when monitoring patients' adherence to a treatment plan (this does not mean the ability to determine a specific dose at a specific time, which at the present time is not scientifically possible) should be at the laboratory's limit of detection (LOD‡). Clinicians ordering the test should clarify these limits with the testing laboratory and determine whether or not it has the capability to detect and report substances below the stated cutoff level. If a laboratory does not have established protocols for reporting LOD for less than cutoff 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 contributing to a positive immunoassay test result. The semisynthetic opioids oxycodone and oxymorphone will not typically be detected even at the 300 ng/mL cutoff. The synthetic opioids, such as fentanyl, meperidine, and methadone, will not be detected by current opiate class immunoassays. A positive immunoassay

*Diversion: diverting drugs from their lawful medical purpose

†The following cutoffs may help to rule out poppy seed ingestion alone: codeine >300 ng/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)[52]

‡Limit of detection (LOD): lowest amount of drug that a laboratory can reliably identify in a specimen; the LOD varies depending on the methodology and the laboratory. For example, if a laboratory has a cutoff for a particular drug of 300 ng/mL and a LOD of 50 ng/mL, the lower limit should be used for clinical purposes.

opiate screen in the context of these prescribed opioids necessitates more specific identification of the substance(s) that account for the positive result.

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. Testing offered by specialized laboratories will be more sophisticated than that offered through hospital laboratories. 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, even when performed by the same SAMHSA-certified laboratory. The absence of SAMHSA certification does not preclude a laboratory from being able to competently perform the required testing for clinical practice, as all licensed laboratories are subject to some degree of proficiency testing, but SAMHSA certification does add to a laboratory's overall competence. All laboratories are not equal, and 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.

Questions for clinicians to ask when initially evaluating a laboratory:

- Ability to talk to someone at the laboratory about specific tests or results
- Cutoff concentrations and LOD reporting
- Turnaround time*
- Sample storage times for both positive and negative samples
- The basic tests/panels included on the laboratory requisition form and the designations required for additional drugs

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.[8;9;36;41;50] The APS/AAPM clinical practice guideline states that insufficient evidence exists to guide precise recommendations on appropriate monitoring intervals, and the VA/DoD guideline states that the frequency of UDT should be based on the risk level of aberrant drug-related behaviors.[9] Therefore, frequency of testing should be determined by clinical judgment, based on a proper assessment and evaluation of the patient, and should comply with state or federal requirements, where applicable.[39;41] However, following a minimum statutory requirement may not be sufficient to meet clinical requirements in all cases. If the patient is displaying aberrant behavior, testing frequency should be sufficient to assist in documenting the appropriate therapeutic intervention to support compliance with the agreed-upon treatment plan. As with any testing, clinicians should be aware that more is not always better—excessive testing is cost prohibitive, can interfere with a patient's healthy daily activities and functions, and can generate needless information that can interfere with, rather than enhance, appropriate test result interpretation.

UDT is commonly included in a written or oral treatment agreement that outlines what the patient can expect of the clinician, and what the clinician will expect of the patient.[53-56] Such an agreement, which describes a clearly understood and well-defined description of treatment boundaries (eg, pill counts, a random or routine 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.[57] The fact that the patient and clinician have agreed to these tests suggests a positive therapeutic alliance. A sample script to use with patients when broaching the sometimes difficult subject of UDT can be found in **Box 1**.

Advocate for Patients

Clinicians can use UDT as an objective tool to assist in advocating for patients with family, workplace, and contested situations. UDT is only 1 of many clinical tools that are important to assess patient adherence to the agreed-upon treatment plan and to help assess patient stability.[36] Examples of situations in which UDT may be used as a tool for patient advocacy include workers' compensation and divorce/child custody cases. UDT used with accurate record keeping and due care can complement other methods used by clinicians 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 inappropriate drug use; UDT results that are in conflict with the patient's self-report should be further investigated, with significant tightening of boundaries as a condition of ongoing treatment with controlled substances (eg, limited dispensing by individual prescriptions or sequential† prescriptions [ie, "Do not fill until _/_/_", if

Box 1. Talking to patients about UDT

Example 1: New patient	
Clinician	One of the things that we offer our patients with chronic pain is urine drug testing. This is a safe and effective means of assisting with risk management, and it is part of our commitment to you as the patient to ensure optimum care.
Patient	Oh, so you mean I don't have to do it?
Clinician	Of course you don't have to do it, but you need to understand that failure to take advantage of this test will severely limit the options that I can safely offer you in terms of medication management.
Example 2: Existing patient‡	
Clinician	Urine drug testing is a safe and cost effective method of helping to manage risk in order to make sure that I'm here next week, next month, or next year when you need me, and to make sure that you get the care you need.
Patient	Do you think that I have a drug problem?
Clinician	I don't necessarily think that you have a drug problem, but in the interest of fairness and balance, testing is something that is now being recommended.

*Turnaround time: the time required by the laboratory to provide final results after the laboratory's receipt of the sample

†While the practice of writing postdated prescriptions to effect sequential dispensing of controlled drugs is unlawful at both the federal and state levels, "Do not fill until_/_/_" federal regulations allow for a series of prescriptions for up to a 90-day supply, all dated on the day written, to be dispensed sequentially by the pharmacist over time at predetermined future dates to assist in controlling a patient's medication use. This is not allowed in all states.

‡In those cases where a long-standing patient is reluctant or refuses to participate in UDT, and is likely to be physically dependent on the opioid class of drug, a significant tightening of boundaries (eg, very limited prescriptions, more frequent follow-up appointments) may serve to encourage formal participation in the UDT process

allowed in your state], increased frequency of appointments, pill counts, referral to or consultation with an addiction specialist and/or other mental health care specialist).[9;35;36;58;59] 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.[35]

A "Universal Precautions"* approach to the assessment and ongoing management of chronic pain patients offers 10 principles (**Table 4**) and a triage scheme for estimating risk that includes recommendations for management and referral.[35;60] Universal Precautions is less about the opioid molecule and more about a balanced approach to the treatment of chronic pain. In addition, there is a multiplicity of screening tools that can be used to assist clinicians in assessing patients;[9] a review describing the benefits and limitation of several such tools was published by Passik and colleagues in the journal *Pain Medicine*.[61] These tools may be helpful to determine which patients are at increased risk for aberrant behavior, including inappropriate or problematic use of prescribed opioids. They may be used to trigger initial and subsequent drug testing until the individual's actual risk can be determined using all the clinical tools available to the clinician, as well as the time necessary to begin to know the patient on a more personal level. Until then, a presumed risk should be used and that risk must never be considered zero—a patient's risk should be reexamined over time as more information becomes available.

Suspected Diversion

Diversion is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale, distribution, or use.[37] When examining whether a patient is taking the medications prescribed or to decrease the risk of diversion, it is essential to know the characteristics of the test being ordered—such as the ability to detect certain drugs—to determine what light it may shed on the patient's use, 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.

UDT cannot diagnose diversion, which is much more complex than the presence or absence of a drug in urine. An inappropriately negative UDT result may indicate drug diversion, but it also opens up a differential diagnosis that may occur secondary to maladaptive drug-taking behavior, such as bingeing, running out early of the prescribed controlled substance, and multiple other factors (eg, cessation or change of insurance coverage, monetary difficulties).[36] This needs to be addressed in a patient-centered context.[36;39] One should always discuss unexpected results with the patient to determine the "motive" behind the abnormal behavior.[60] A negative urine for a prescribed drug should not be interpreted as definitive evidence of criminal behavior, such as diversion. In addition, quantitative assessment of a drug analyte in urine does not provide reliable evidence of 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, tightening of treatment boundaries, or referrals. 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.[62;63] 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;36;41;49;62-65] Likewise, the appearance, ethnicity, language, or culture of a patient is not a reliable indicator of risk of aberrant drug-related behavior; a rational protocol of performing UDT on all patients receiving or being considered for prescription of controlled substances can help to validate and destigmatize patients.

Table 4. The 10 steps of Universal Precautions[35;60]

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] • Analgesia, Activity, Adverse reactions, and 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.
[a]Passik SD, et al. *Clin Ther.* 2004;26:552-561.

New Patients Already Receiving a Controlled Substance

In addition to history, physical examination, contacting past providers, 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 may increase both clinician and patient acceptance of this test by normalizing the clinical context of its use. When clinicians 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

*Universal Precautions in pain management: recommendations to guide patient assessment, management, and referral to improve patient care, reduce stigma, and contain risk[35;60]

confirm their presenting condition, or who are reluctant to undergo diagnostic tests, including UDT, may be poor 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 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 providers. 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.[60] In the authors' opinion, prescribing controlled substances to patients who are "philosophically opposed" to UDT is relatively contraindicated.[57]

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 is a potential warning sign. 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, an individual's analgesic response to a particular drug may be affected.[66] 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. However, as a general rule, a clinician 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 provider is not available, and may insist on being seen immediately because they are late (for their flight, meeting, child's soccer game, etc).[67] 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, 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.[64;67-69] Often, however, it may be easier to identify aberrant behaviors than to understand the causes or motives behind them.[70] Patients who are not addicted to, misusing, or diverting drugs may display aberrant behaviors; 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*.[69;71] Although no single 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 is the hallmark of pseudoaddiction.[70] Indeed, iatrogenically driven aberrant behavior can be the result of overly proscriptive treatment agreements, excessive UDT, or other iatrogenically driven mechanisms. Structure and support are often difficult balances to strike, especially in patients who have demonstrated aberrant behavior. Beware the patient who promises to "stop using cocaine if you would only increase the pain medications," as this is an easy trap for the inexperienced clinician to fall into. Medication dose increases and loosening of boundaries should only occur *after* the patient demonstrates discontinuation of cocaine use.

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 may 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.[41;57] 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 treatments of first choice, they must also not be considered as agents of last resort.[57] Implementing monitoring strategies, including UDT, becomes especially important when managing patients who have substance-use histories.[41;57]

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 element of primary care.[39] UDT should be considered as a part of the evaluation of any new patient who is taking controlled substances or for whom controlled substances may be prescribed, and it should be discussed with all patients presenting with chronic pain in order to normalize this strategy in your practice. Even in the absence of controlled substances, UDT can be an effective tool in clarifying otherwise challenging cases where treatment goals are not being achieved.

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, or a significant family history.[72] 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 also little evidence to the contrary. Therefore, routine screening for a personal or family history of misuse or addiction in all patients is appropriate before prescribing any medication, especially a controlled substance.[72] 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.[72]

A history of substance misuse does not preclude appropriate treatment with any medication, including a controlled substance, but it does increase risk.[9;35] When indicated (eg, opioid analgesia to relieve pain), it requires a treatment plan with firmly defined boundaries, as well as clearly defined endpoints of success.[9;35] Clinically, a patient in recovery

*Pseudoaddiction: an iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain control

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.[9;53;57] A patient with active addictive disease must engage in a program for recovery to increase the success of the treatment of his or her pain syndrome before chronic prescribing of controlled substances can be contemplated. Chronic pain problems cannot be solved in the face of active, untreated addiction.[60]

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 reason for the treatment is not for the maintenance or detoxification of a concurrent opioid substance-use disorder.[24] 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.

In some cases, clinicians find themselves entering into chronic opioid therapy almost by accident, at which time it can often be difficult to establish good boundaries and assess risk appropriately. Therefore, before writing the first prescription, clinicians should be thinking about risk management, which can include discussions about UDT. If the patient claims to be philosophically opposed to or uncomfortable with UDT, the clinician can explain that this restricts his or her ability to do a good job in managing that patient and may limit the options available for optimal medication management.

When Making Major Changes in Treatment

Modification of therapy, particularly dose increase, should depend on the evaluation of progress toward stated treatment objectives (eg, decreased pain and increased function) while monitoring for side effects and aberrant behaviors. If these 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 increased risk for misusing medications (eg, personal or significant family history of substance misuse or addiction, or comorbid psychiatric disorder).[53;56] Unexpected positive or negative UDT results, which are verified, where necessary, through discussion with the laboratory and that cannot be clarified through discussion with 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 or someone who is knowledgeable in addiction medicine.[53;56;72] For clinicians who do not have available formal referral resources in this often under-serviced area of pain and addiction medicine, informal consultative support should be sought.

INTERPRETATION OF UDT RESULTS

UDT in clinical practice, like any other medical test, should be performed to direct and ultimately improve patient care.[60] 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. Clinicians should use UDT results in conjunction with other clinical information. Consultation with an individual knowledgeable in UDT interpretation (eg, laboratory director, toxicologist, or knowledgeable colleague) 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 in a relevant clinical context.[25;49]

IMMUNOASSAY CROSS-REACTIVITY

In a perfect world, UDT would be able to accurately report what is present and confidently report what is absent in a urine sample. However, detection of a particular drug by a drug-class–specific immunoassay (both POC and automated laboratory-based) 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.[17] For example:

- Tests for cocaine react principally with cocaine's primary metabolite, BEG. These tests have low cross-reactivity with other substances and, therefore, presence of BEG 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 (eg, "chiral" chromatography) (see page 13 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 opioids and an inability to detect 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).[17;24;73;74] A negative result does not exclude use of these opioids, but the ability of opiate immunoassays to detect semisynthetic opioids varies among assays because of differing cross-reactivity patterns. Specific immunoassay tests for some semisynthetic/synthetic opioids may be available (eg, oxycodone, buprenorphine, methadone/EDDP).

Therefore, for clinical purposes, the cocaine assay would be considered very reliable, while the amphetamine assay would be less reliable in predicting use of the drug, and the opiate assay would be unreliable in predicting use of semisynthetic/synthetic opioids. The more definitive combined laboratory-based chromatographic technologies are not subject to cross-reactivity. Therefore, 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

*Recovery program: an ongoing process to help the patient develop coping strategies and tools for abstaining from drug use and then maintaining abstinence

that the correct test/profile is used. Many laboratories that service the pain management community have adopted a screening and identification protocol involving more definitive testing such as GC/MS or LC/MS, which avoids the cross-reactivity limitations of POC and laboratory immunoassays.

Cross-reacting compounds can also be structurally unrelated to the standardizing compound. For example, several quinolone antibiotics (eg, levofloxacin, ofloxacin) can potentially cross-react with some common opiate immunoassays, despite no obvious structural similarity with morphine.[75;76] Quinolones are not misidentified as opiates by GC/MS or LC/MS. There have also been cases of cross-reactivity between some fentanyl immunoassays with the antidepressant trazodone,[77] and some PCP immunoassays with the antidepressant venlafaxine.[79] Examples of other agents that can cross-react with immunoassays are shown in **Table 5.** Because testing technology is constantly evolving and varies by manufacturer, 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. Review all positive results with the patient to explore possible explanations. All unexpected results should be verified with the laboratory to ensure their accuracy.

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.[25] 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.[25] There is currently no scientifically validated relationship between the concentrations reported in the urine and the doses taken of prescribed drugs.[49;66;91;92]

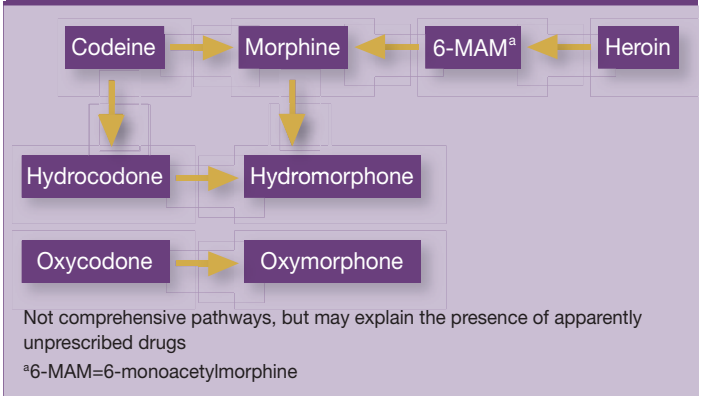
Table 5. Examples of potential false-positives due to cross-reacting compounds for certain immunoassays

Interfering drug	Immunoassay affected[a]
Quinolone antibiotics (eg, levofloxacin, ofloxacin)[75;76]	Opiates
Antidepressant trazodone[77;80]	Fentanyl; MDMA (Ecstasy)
Atypical antipsychotic quetiapine[83]	Methadone
Antidepressant venlafaxine[79;81]	PCP
Dextromethorphan[88]	PCP
Tramadol[89]	PCP
Selegiline (for Parkinson's disease)[78]	Amphetamine
Diet pills (eg, clobenzorex, fenproporex)[85;86]	Amphetamine
Promethazine (for allergies, agitation, nausea, vomiting)[87]	Amphetamine
l-methamphetamine (over-the-counter nasal inhaler)[85;86]	Amphetamine
Antidepressant bupropion[82]	Amphetamine
Antiretroviral efavirenz[84]	THCA
Proton pump inhibitors (eg, pantoprazole)[90]	THCA

[a]Only some immunoassays are affected; cross-reactivity patterns change constantly as reagents are refined to address these issues

MDMA=methylenedioxymethamphetamine; PCP=phencyclidine; THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

Figure 1. Examples of metabolism of opioids



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

[a]6-MAM=6-monoacetylmorphine

Any unexpected positive result for illegal or unprescribed drugs 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.[35] Although the substance-use disorder does not diminish the patient's complaint of pain, it does complicate the management of it.

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.[50] However, a morphine-positive UDT may also result from codeine and from morphine in foodstuffs (eg, poppy seeds in some breads/confectionery).[10;25;49;93] 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**).[10] 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.[10;26;94] 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.

Positive Results With a Medical Explanation

In certain cases, a patient may have a positive UDT result because of medication prescribed by another clinician or use of OTC products.[10] Clinicians 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 results.

Several examples of positive results with a medical explanation are listed on the following page.

Opioid metabolism: (See **Figure 1**)

- Codeine is metabolized to morphine, so both substances may occur in urine following codeine use:[10;49;50]
  - 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 alone.
    - Codeine metabolizes to morphine, but the reverse does not occur.
    - Morphine preparations may have small amounts of codeine as an impurity from manufacture (generally about 0.04%).[95]
  - Codeine alone is possible because a small proportion of patients (<10% of the Caucasian population) lack the necessary activity of the cytochrome P450 (CYP) 2D6 enzymatic pathway to convert codeine to morphine.[96] Patients on certain CYP2D6-inhibiting drugs may also lack the ability to convert codeine into morphine, potentially interfering with UDT interpretation, and reducing codeine effectiveness.
- Morphine may be metabolized to produce small amounts (generally <5%) of hydromorphone.[51;97-103]
- Hydrocodone may be metabolized to small quantities of hydromorphone.[104;105]
- Codeine may be metabolized to small quantities (generally <15%) of hydrocodone.[106]
- Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone.[3;107] 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, indicating that this is a metabolite rather than a parent compound.[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, this should generally not be detectable with UDT).[3]
  - Oxycodone preparations may have small amounts of hydrocodone as an impurity from manufacture (generally <0.01%).[108]

Cocaine: Cocaine is a topical anesthetic clinically used in certain trauma, dental, ophthalmologic, and otolaryngologic procedures.[10] A patient's urine may test positive for the cocaine metabolite, BEG, 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 clinician. There is no structural similarity between other topical anesthetics that end in "caine" (eg, prilocaine, lidocaine) and cocaine or BEG; therefore, cross-reaction does not occur.[10] A positive UDT result for the cocaine metabolite, in the absence of a medical explanation, should be interpreted as due to deliberate exposure to cocaine.[3] Cocaine itself can be detected by GC/MS only with very recent use because of a short half-life.

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 Parkinson's disease. Knowledge of potential sources of amphetamine and methamphetamine can prevent misinterpretation of results.

The traditional GC/MS criteria for reporting a positive methamphetamine result is not sufficient to distinguish methamphetamine use from use of OTC products. Methamphetamine exists as 2 isomers that are designated *d*- and *l*-.[10] 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. This must be specifically requested of the laboratory.

For example, the OTC Vicks® Inhaler marketed in the United States contains *l*-desoxyephedrine (*l*-methamphetamine).[10] Patients whose management includes UDT should be advised not to use the Vicks® Inhaler or similar OTC preparations containing this agent because they will 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.

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 clinician.

A 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.[25;50] 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.

Health care professionals should be aware of the time taken for drugs to be absorbed and ultimately eliminated from the body. Time of last use and quantity of drug(s) taken can be helpful in interpreting UDT results.

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 (**Figure 1**). For example, a patient who is prescribed codeine may show trace quantities of hydrocodone that may not represent hydrocodone use.[106] Detection of minor amounts of hydrocodone in urine containing a high concentration of codeine

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

†In this context, adherence testing should not be seen as an assessment of drug dose taken or frequency of use, but it should be considered a general reflection of the patient's compliance with the previously agreed-upon treatment plan. In most clinical settings, it is impossible to know, with any degree of certainty, exactly how much medication a patient is taking.

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.[104;105] 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 unexpected 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 help 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 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 (**Table 6**). In this case, a 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, after verifying this unexpected result with the laboratory.

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 using only a portion of the prescribed medication (potentially hoarding or diverting the rest). While it is tempting to think that quantitative UDT results might clarify these issues, at the present time neither blood nor urine drug concentrations have been scientifically demonstrated to answer these questions. 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 or hydromorphone (**Table 7**), unless an immunoassay specifically directed toward these particular molecules is used.[10] It is possible that some semisynthetic opioids, even at high concentrations, will be inconsistently detected by the opiate immunoassay tests because of incomplete cross-reactivity. In a 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.[109] Most respondents were unaware that oxycodone is not reliably detected by most opiate immunoassays.[109] 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.[45]

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

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**). Both immunoassay and more definitive laboratory-based testing for benzodiazepines pose significant challenges, in both detection and clinical interpretation.

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 in sufficient quantities to be detected
The patient has not used the drug/medication at all
The test used was not sufficiently sensitive to detect the drug/medication at the concentration present
Clerical/laboratory errors caused a positive UDT result to be reported as negative
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 patient has diverted the medication

Concentration Effects: It is important to know the threshold concentrations that your laboratory uses when interpreting a report of "no drug present."[1;50] A drug may be present in the sample, but below the laboratory's reporting cutoff concentration. Measuring random 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 may be much more difficult to interpret.

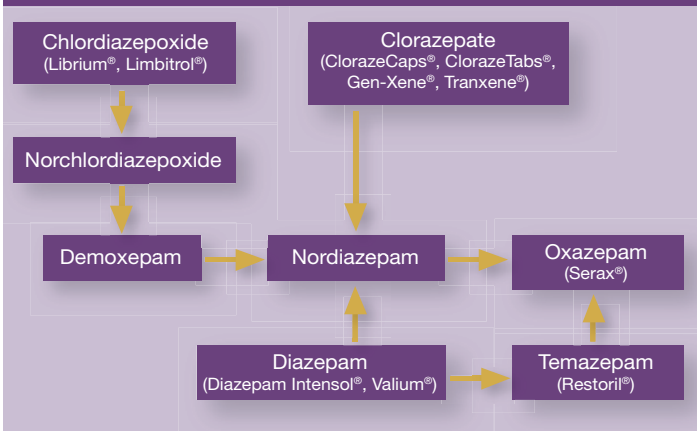
Amount of Drug Taken: At this time, there is no scientifically validated relationship between the amount of drug taken, the amount excreted, and the concentration of the drug recovered in urine. Therefore, for a variety of reasons, UDT cannot indicate the amount of drug taken, when the last dose was administered, or the source of that drug.[4;49]

Recently, some laboratories have offered technology to calculate a normalized urine drug concentration value based on the patient's height and weight and the specimen's specific gravity and/or creatinine

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	• Methadone
	• Oxymorphone	• Tapentadol
	• Buprenorphine	

Figure 2. Some examples of benzodiazepine pathways of metabolism



concentration to extrapolate the dosage consumed. However, many other factors can influence the absorption, distribution, metabolism, and elimination of a drug. These include genetic polymorphisms (eg, enzymatic variability), renal and hepatic function, disease states, body surface area and muscle mass, cardiac output, drug-drug interactions, drug-food interactions, and age. In addition, even patients who adhere to a drug schedule of 3 times a day, for example, will rarely take their medication at exactly 8-hour intervals, and factors such as additional medication occasionally required for breakthrough pain are difficult to consider. Therefore, at this time, UDT measurements should not be used to interpolate backward and make specific determinations regarding dose of the prescribed drug. Software and laboratory products have not been validated scientifically and peer reviewed in the medical literature. Interpreting UDT beyond the current scientific knowledge may put clinicians and their patients at medical and/or legal risk.[66;92]

Other laboratories compare quantitative urine opioid results to standardized urine concentrations in very large medication-using populations to report a measure of adherence with drug use (ie, "in range," "low," or "high").[110] However, the mathematical models used to produce the range of expected values for pain medications vary and are not subject to consensus. The assumption that this "standardized population" is "known to be compliant" with their medication use is fundamentally limited. Therefore, individual patient comparisons with respect to compliance assessment are uncertain.

MYTHS

Passive Inhalation

Passive smoke inhalation does not explain positive marijuana results at typical cutoffs (50 ng/mL).[10;25] 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.). Synthetic 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.[111] 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 anti-emetics.[112;113] Another drug currently available in Canada (in clinical trials in the United States) is buccal 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.[114-116]

Smoked cannabis, orally administered Marinol®, and buccal Sativex® all produce positive immunoassay and GC/MS 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 positive GC/MS result for THCA because it does not contain THC.[112] There have been reports of positive urine immunoassay tests for cannabinoids in patients receiving proton pump inhibitors, such as pantoprazole (Protonix®).[90] However, a more definitive test such as GC/MS or LC/MS can rule out this immunoassay 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.[117;118] However, multiple studies have found that the THC concentrations typical in hemp products are sufficiently low to prevent a positive immunoassay result.[117;118]

There have been documented cases of cocaine ingestion by drinking tea made from coca leaves.[10;119] 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 FDA regulations. However, these products remain a problem, and patients should be advised not to ingest hemp products or coca tea.

EMERGING DRUGS OF ABUSE

More recently, synthetic cannabinoid molecules such as JWH-018 have seen a resurgence of interest in street drug use as "designer drugs" that produce "legal highs."[120-122] The herbal marijuana alternatives, like K2 or Spice, are a group of herbal blends that contain a mixture of plant matter in addition to chemical grade synthetic cannabinoids.[121] The current legal uncertainties with many of these molecules have led to challenges at both the detection and interdiction levels. The synthetic cathinones, commonly called "bath salts," have resulted in emergency department visits throughout the United States for severe agitation, sympathomimetic toxicity, and death.[121;123] Laboratories are currently developing more definitive methods to identify these molecules.[120]

Buprenorphine has also become more abused as its availability in the office-based treatment of opioid addiction has increased.[124;125] However, many laboratories do not routinely test for buprenorphine.

ALTERNATIVE TECHNOLOGIES FOR DRUG TESTING: BENEFITS & LIMITATIONS

Drugs can be detected in many other biologic specimens, including hair, oral fluid, blood, sweat, and nails.[126] Several specimens are available as alternatives to urine for drug testing, including blood, oral fluid, and hair.[1;85] This section will briefly compare with urine the pattern of information offered by each specimen regarding drug use over time. In addition, the particular strengths and weaknesses regarding the type of information that may be obtained, ease of collection, degree of invasiveness, analytical and testing considerations, as well as interpretation of results will be examined.[5;7;85;126]

The window of drug detection for urine, hair, oral fluid, and blood are not identical, but the results from each specimen can complement each other (**Figure 3**).[85;91;127] 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.[128-130] Some drug classes are more difficult to detect than others for a given type of specimen.[1;127]

Blood: Blood testing can detect low levels of substances and is a better sample for the legal assessment of an actively intoxicated patient.[1] However, it is an invasive and expensive procedure, has a window of detection that is limited to current drug use, and is not as amenable to rapid screening procedures.[85]

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.[22;85;128;131-133] 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.[85;134] Similarly in pain clinics, the pattern of licit and illicit drugs and metabolites observed in oral fluid paralleled results reported for urine, with some minor differences in detection rates for different drug classes.[135;136]

Oral fluid is composed of saliva, mixed with buccal and mucosal transudates, cellular debris, bacteria, and residue of ingested products.[128] Oral fluid specimens are generally considered to reflect circulating drug concentrations because salivary glands are highly perfused, allowing rapid transfer of a drug from blood to oral fluid.[128] Thus drugs are detected earlier in saliva than in urine, but for shorter time periods.[22] Oral fluid is generally useful for detecting drugs for up to 4 hours, but some drugs can be detected for up to 24 hours.[85;127] It is amenable particularly to post-accident testing.

Collection procedures are not standardized and can affect drug concentrations.[22] Specimens are collected by having the patient expectorate into a container, or by using a commercially available collection device. Adsorption of the drug to the material of a collection device also introduces issues of drug recovery compared with the original oral fluid.[22;128;137] 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.[22]

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.[22;128] It has not yet been determined, however, whether adulterants exist that can be safely placed in the mouth to produce 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.[22;128;137]

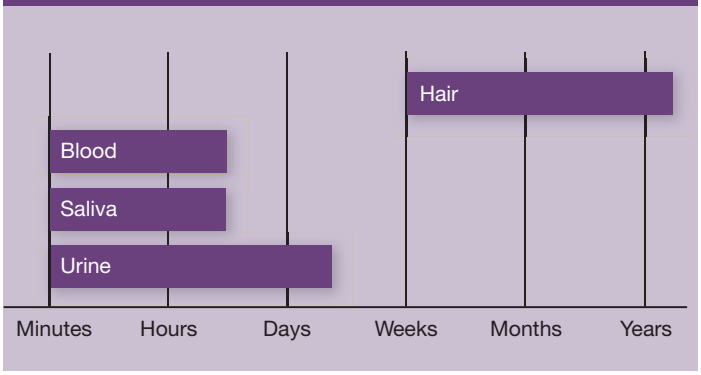
Hair: The disposition of drugs in the body includes incorporation into growing hair.[138] Hair may be useful to objectively document past drug use, but it is usually inefficient for clinical testing.[85;138] Testing hair can extend the window of detection for a drug to weeks or months depending on the length of the hair tested.[85;127;139] 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;49;126]

Several mechanisms for incorporation of drugs into hair have been proposed.[138] 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.[129;138] The ability of hair testing to distinguish drug use from external contamination (eg, drugs in smoke or the environment) remains controversial.[126;138] Measuring metabolites and washing hair samples can help prevent false-positive results from external contamination.[138]

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;49;50;85;126] Other disadvantages of hair analysis to validate drug use include irregular growth, labor-intensive sample preparation, low analyte concentrations, and excessive cost.[7;50;126] 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.[126] However, methods for evading UDT do not affect hair analysis, and collection can be performed under close supervision.[139]

Alternative Specimens Summary: New diagnostic tests are developed to improve clinical utility, accuracy, and convenience for the patient and/or clinician, and to decrease expense and turnaround time.[131] Different biologic matrices have different cutoff concentrations for various drugs, but criteria for specimen validity have yet to be defined.[127] At present, much of the available knowledge on drug

Figure 3. Relative detection times of drugs in biologic specimens[91]



disposition in biologic matrices has been generated from single- or multiple-dosing studies, but information is limited in chronic users.[128] 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.[128] Oral fluid is promising and may be a valuable complement to UDT in clinical pain management settings.[140]

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) and ethyl sulfate (EtS) are conjugated metabolites of alcohol that can persist in the urine for several days (although there is wide inter-individual variability).[141-146] Thus EtG or EtS are markers to detect alcohol use or exposure, and the tests have recently become commercially available. They may be useful to help motivate patients to remain or become abstinent from alcohol by providing objective evidence of abstinence. The tests are not useful to measure a reduction in alcohol intake in the nonabstinent user.

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 stuffs. Such incidental exposure can lead to a positive EtG or EtS test even when alcoholic beverages were not consumed. There are no established cutoffs, and various laboratories may offer different interpretations.[141] Generally, EtG concentrations below 100 ng/mL indicate total abstinence from alcohol, 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. Significantly elevated EtG concentrations can result from hand washing with common hand disinfectants (eg, Purell®, 62% ethyl alcohol).[147] EtG and EtS cutoffs of 500 ng/mL were shown to be able to distinguish between ethanol consumption and 4-times daily use of high ethanol content mouthwash.[145] EtG and EtS test results should be used as a diagnostic aid in the total management of the patient. Clinicians 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 issued a boxed warning which states:[148]

> *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 unsupportable 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 for chronic pain

Because substance-use disorders are not uncommon, UDT should be considered a core clinical tool in primary care to appropriately manage risk. The clinician can use a discordant UDT result to motivate patient behavioral change. However, testing without an appropriate strategy for interpreting results can do harm. Clinicians must be aware of the limitations of UDT, and not rely on test results alone to make irreversible patient care decisions or decisions that have other potentially negative ramifications for the patient. A working relationship with the testing laboratory or POC device provider is essential to accurately interpret UDT results. Most importantly, a clinician should strive for a relationship of mutual honesty and trust with the patient when using UDT in his or her clinical practice. Ideally, the use of UDT should be a consensual process between clinician and patient that is designed to assist in managing patient care. There should always be a logical relationship between the result obtained and the clinical course correction, if any, that results.

UDT is something we should do ***for*** our patients rather than something that is done ***to them***.

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GLOSSARY

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

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 μ receptors

POC: Point-of-care on-site testing designed to be used where the sample is collected using either instrumented or noninstrumented commercial devices

Pseudoaddiction: An iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain control

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 other than as directed or as indicated, whether willful or unintentional, and whether harm results or not

Turnaround time: The time required by the laboratory to provide final results after the laboratory's receipt of the sample

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

ABBREVIATIONS

6-MAM	6-monoacetylmorphine
AAPM	American Academy of Pain Medicine
APS	American Pain Society
BEG	benzoylecgonine
CLIA	Clinical Laboratory Improvement Amendments of 1988
CNS	central nervous system
CYP	cytochrome P450
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMR	electronic medical records
EtG	ethyl glucuronide
EtS	ethyl sulfate
FDA	US Food and Drug Administration
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
VA/DoD	Department of Veterans Affairs/Department of Defense

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:
    - Amphetamines (including ecstasy)
    - Benzodiazepines
    - Marijuana
    - Methadone
    - Opiates
    - Oxycodone
    - Cocaine
  - Additional tests may be added as needed
  - Verification or specific identification tests may be added, as necessary (eg, GC/MS or LC/MS)
- 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:

Amphetamines Amphetamine Methamphetamine Phentermine	***Barbiturates*** Amobarbital Butabarbital Butalbital Pentobarbital Phenobarbital Secobarbital	***Benzodiazepines*** Alprazolam Chlordiazepoxide Clonazepam Clorazepate Diazepam Flurazepam Lorazepam Oxazepam Temazepam
Opioids Buprenorphine Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Meperidine Methadone Morphine Oxycodone Oxymorphone	***Miscellaneous*** Carisoprodol Meprobamate *Illicit Drugs* Cocaine/Crack Heroin/6-MAM MDA MDEA MDMA Marijuana Paramethoxy-amphetamine	

- Specimen collection:
  - Random collection is preferred
  - Unobserved urine collection is usually acceptable
  - Check urine temperature, pH, and creatinine concentration
  - If tampering is suspected, consider ordering an "adulteration panel" from your laboratory
    - Submit the suspect sample as well as a fresh sample
- UDT results:
  - Consult with laboratory regarding ANY unexpected results that are contested by the patient
  - 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 clinician-patient relationship and to support positive behavior change
  - Chart results and interpretation

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