Urine Drug Testing in Clinical Practice

The Art and Science of Patient Care

EDITION 6

Target Audience: Healthcare professionals who treat patients with chronic pain

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PROGRAM OVERVIEW

There remains significant controversy as to whether some well-selected and carefully monitored patients with chronic pain experience improved function, meaningful pain relief, and improved quality of life from opioid therapy. But for others, opioid treatment may result in misuse, abuse, and diversion; and may not improve function. Therefore, proper prescribing of controlled substances is critical to patients' health and to safeguard society against abuse and diversion.

A number of organizations and agencies have developed recommendations and guidelines that include the use of urine drug testing (UDT) as a tool to assist clinicians to responsibly prescribe opioids when managing chronic pain; for example, clinical practice guidelines for chronic pain management published by the American Pain Society/American Academy of Pain Medicine and the Department of Veterans Affairs/Department of Defense include a provision for UDT. However, neither guideline provides instruction for how UDT should be performed in clinical practice nor how to interpret UDT results. In addition many state medical boards/agencies have developed policies or guidelines that require or suggest the use of UDT in certain situations.

Despite potentially serious outcomes from UDT for pain patients (eg, dismissal or changes to the treatment plan), clinicians often lack training in the use of UDT, and UDT is often underused or used inappropriately in clinical practice. Before ordering UDT, clinicians should understand methods of testing, the potential benefits and limitations of UDT, and how to interpret results, so that they can rationally employ patient-centered UDT in clinical practice. This monograph will assist clinicians to appropriately use UDT to improve patient care.

LEARNING OBJECTIVES

Healthcare professionals participating in this educational activity will be able at its conclusion to:

1. Develop a testing strategy to utilize UDT in the care of patients with chronic pain.
2. Distinguish between types of UDT and formulate practical strategies to determine the appropriate test to order and accurately interpret UDT results.
3. Create a practice plan to maximize the utility of UDT results by charting the interpretation, discussing unexpected results with patients, and consulting with a toxicologist/laboratory director when necessary to interpret unexpected results.

TARGET AUDIENCE

Healthcare professionals who treat patients with chronic pain

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2. Read the monograph.
3. Complete the Online Post Test, Evaluation, and Credit Application form at **www.udtmonograph6.com/credit.html**
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INTRODUCTION

There remains significant controversy as to whether some well-selected and carefully monitored patients with chronic pain experience improved function, meaningful pain relief, and improved quality of life from opioid analgesic therapy. However, opioids are controlled substances that also have the potential for misuse, abuse, addiction, and diversion. A number of organizations and agencies have developed recommendations and guidelines that include the use of urine drug testing (UDT) as a tool to assist clinicians to improve patient care and responsibly prescribe opioids when managing chronic pain.[1-4] For example, 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 (VA)/Department of Defense (DoD)—include a provision for UDT.[1;2] However, neither provides instruction for how UDT should be performed rationally in clinical practice.[1;2] In addition, many state medical boards/agencies have developed policies or guidelines that require or suggest the use of UDT in certain situations.

Any test, including UDT, must meet the basic standards of medical necessity if it is to be a credible element of clinical care.[5] All 3 of the following elements must be addressed:[5]

- Why was the test ordered?
- What results were obtained?
- What changes in clinical course were made (including staying the course, if appropriate) as a result of these test results?

Failure to ask, answer, and document in the medical record these key elements of medical necessity may leave the clinician open to medico-legal exposure.[5]

Any test, including UDT, must meet the basic standards of medical necessity if it is to be a credible element of clinical care.

In addition, not understanding the limitations of testing, overinterpreting the results, or using UDT results in isolation could lead to clinical decisions that are detrimental to both the clinician and the patient, such as adversely altering or even terminating patient care.

The sixth edition of this monograph, first published in 2002, serves to address some of the current issues and controversies surrounding UDT. It describes 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 develop and implement a clear patient-centered testing strategy to incorporate tests into their practices as part of a balanced approach to optimal medical care and risk management, especially when prescribing controlled substances. The monograph will help clinicians to decide when to order UDT, what questions they should reasonably expect to answer, and the type of tests to order to answer those questions. It will explain how to interpret results in order to use UDT as a clinical tool to improve patient care. The monograph will also provide advice for interacting with the testing laboratory (at the outset of testing and thereafter, as necessary) to ensure that the tests are being used optimally to enhance patient care.

BACKGROUND

The traditional clinical role of 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.[6;7] When used effectively, however, UDT is more than just a verification tool and has many useful clinical applications in patient-centered care.

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 likely to be positive for a broad 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 monograph.

The term urine drug "screening", while often used, is a misnomer, since it may imply screening for all drugs.[6;8] In reality, it is not possible to prove the presence or absence of all drugs, and the testing process is open-ended and evolving.[9] There is no "standard" UDT that is suitable for all purposes and settings—rather, a multitude of options exists that clinicians should adapt to their particular clinical needs.[6]

Traditionally, the 2 main types of UDT—which are often used in combination—were:

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

Today, a variety of more comprehensive approaches are used, often by laboratories specializing in the pain management setting (ie, pain management laboratories†), which have emerged to meet the challenge of utilizing UDT with complex chronic pain patients whose pharmacotherapy can overlap with many drugs of abuse. The technologies used by these laboratories are described on pages 4-6. However, the aim is not to test for every drug that is available for analysis, but to do medically necessary and reliable testing for those drugs that are most likely to impact clinical decisions.[10]

UDT typically detects the parent drug and/or its metabolite(s) and, therefore, demonstrates recent use of prescription medications, unprescribed drugs, and illegal substances.[6;11;12] 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 20-22.[11;13]

URINE DRUG TESTING METHODS

For most clinical and forensic applications, initial qualitative 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, LC/MS, or LC-MS/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, LC/MS, or LC-MS/MS testing. The UDT method chosen should be a function of the questions that need to be answered. It is important that clinicians understand the methods for UDT in order to rationally order and interpret results.[1]

IMMUNOASSAYS

The immunoassay drug tests, which are designed to classify substances as either present or absent according to a predetermined cutoff threshold, remain the most common methods used in clinical care. Immunoassays are based on the principle of competitive binding, and use antibodies to detect the presence of a particular drug or metabolite or class of drugs or metabolites in a urine sample.[14] 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 has some proportional relationship 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 clinical purposes, identical). Immunoassays are also subject to cross-reactivity;[14] ie, substances with similar, and sometimes dissimilar, chemical compositions may cause a test to appear positive for the target drug or drug class (see pages 15-16 for more details). Samples that test positive by immunoassay for classes of drug may need to be tested in the laboratory by a more definitive method if specific identification of the drug is required (such as contested results‡).

* In forensic models of testing, the terms "confirmation" or "confirmatory testing" are used, but clinical testing with combination technologies like gas chromatography/mass spectrometry (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.

† Pain management laboratory: although the term has not yet been specifically defined, in the authors' opinion a pain management laboratory is a specialized toxicology laboratory combining the patient-centered goals of a clinical laboratory with the precision seen in the forensice world. The testing profiles include both parent drugs and metabolites in multiple classes of substances that are either potential therapeutic agents (both prescribed and nonprescribed) or likely abused substances. More than 40 substances (which are evolving) need to be available in the testing, which is also coupled with the availability of experienced toxicologists or clinical pharmacists for interpretation and consultation. An effective laboratory is a unique blend of clinically relevant testing and diagnostic services.

‡ Contested results: for the purposes of this monograph, a contested result is one where the patient disagrees with the UDT report/interpretation

Point-of-Care Testing

A number of single-use noninstrumented immunoassay devices (eg, test strips/cups) 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 clinician, sometimes at the expense of accuracy and reliability.[15-19] POC testing may be particularly useful to quickly evaluate new patients for abuse of illegal drugs. Clinicians who elect to use POC testing need to consider regulatory requirements; safety, physical, and environmental requirements; benefits and costs; staffing; and documentation.[16;20] 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.[16]

Noninstrumented POC devices commonly use immunochromatographic methods that produce visually read results.[15;21] 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.[21;22] 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.[15;19;23;24] These portable tests are typically performed by health care workers whose roles include a variety of nontesting-related duties.[15]

Although POC tests are designed to be simple to use, they utilize complicated technology and still require proficiency to produce acceptable performance.[15;21;24-26] The operators of POC testing must use good laboratory practice to enable them to produce reliable, clinically useful results.[15] Training of users should include quality control issues and recognition of any device limitations.[24] 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 carefully evaluate 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.[15]

Although performance of POC tests have minimal requirements (simply that of following the manufacturer's recommendations), studies have demonstrated that those performing POC tests often do not adhere to manufacturers' recommendations and variable error rates occur.[18;27] 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."[15]

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.[17] 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, or the absence of any prescribed drugs, more sophisticated laboratory tests such as GC/MS or LC/MS may need to be used.

Some physician offices or groups have established in-house laboratories with advanced chromatographic instrumentation, which in some states must be overseen by a qualified laboratory director. Such a laboratory director generally only comes to the site for a few hours each month, so quality in these cases may be questionable. Practices that are considering establishing an in-house laboratory must carefully consider the ramifications of financial benefit from a test that they are ordering. In the past, it has been demonstrated that physicians who have in-office imaging equipment, such as for chest radiography, obstetrical ultrasonography, and lumbar spine radiography, obtain imaging examinations 4.0 to 4.5 times more often than physicians who refer patients to radiologists, and charged significantly more than radiologists for imaging examinations of similar complexity.[28] An article in the *Wall Street Journal* described one pain specialist who started to perform in-office laboratory drug testing in 2010—by 2012 drug testing accounted for 80% of his medical practice's Medicare payments.[29] It is essential that any test is medically necessary and performed for the benefit of the patient, not because it is financially rewarding—this could leave the clinician open to investigation and successful prosecution for fraud.

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 where class alone is insufficient; for example, that it actually is prescribed morphine that is accounting for the positive immunoassay class response (rather than some other opioid or cross-reacting substance); (2) to identify drugs not otherwise included in other tests; and (3) when results are disputed by the patient (ie, contested results).

While GC/MS has traditionally been the gold standard chromatographic technique for specific drug identification, laboratories that specialize in the needs of the pain management community have introduced other combinations of chromatographic testing (eg, LC-MS/MS), which also allow detection of both parent

Table 1. Example of drugs/metabolites that are commonly detected in a pain management panel

Drug or drug class	Drugs and/or metabolites[a] included
Amphetamines	Amphetamine
	Methamphetamine
	MDMA (Ecstasy)
	MDEA (Eve)
	MDA
	Phentermine
Barbiturates	Butalbital
	Phenobarbital
Benzodiazepines	Alprazolam
	Clonazepam
	Diazepam
	Flurazepam
	Lorazepam
	Nordiazepam
	Oxazepam
	Temazepam
Cocaine	Benzoylecgonine
Heroin	Heroin (diacetylmorphine)
	6-MAM
	6-acetylcodeine
Marijuana	THCA
Opioids	Buprenorphine
	Norbuprenorphine
	Codeine
	Norcodeine
	Dihydrocodeine
	Fentanyl
	Norfentanyl
	Hydrocodone
	Norhydrocodone
	Hydromorphone
	Meperidine
	Normeperidine
	Methadone
	EDDP
	Morphine
	Oxycodone
	Noroxycodone
	Oxymorphone
	Tapentadol
	Tramadol
	O-desmethyl-tramadol
	N-desmethyl-tramadol
PCP	PCP
Carisoprodol	Carisoprodol
	Meprobamate
Anticonvulsants	Gabapentin
	Pregabalin

6-MAM=6-monoacetylmorphine; EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; MDMA=3,4-methylenedioxymethamphetamine; MDA=3,4-methylenedioxyamphetamine; MDEA=3,4-methylenedioxyethylamphetamine; PCP=phencyclidine; THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

[a] For some drugs that are rapidly metabolized, the metabolites may be more important than testing for the parent drug

drugs and metabolites.[10;30] Unlike traditional screen/confirmation techniques (where GC/MS was used to confirm the results from immunoassay screening), the LC-MS/MS techniques used in pain management testing today apply chromatographic testing methodologies in such a way as to perform comprehensive specific drug identification of a variety of drugs of interest..

There is no standardization between different pain management laboratories in terms of the type of tests that they perform, what drugs and metabolites are included and at what limit of detection (LOD), how they report the results, and what, if any, interpretation is offered with the test results. Table 1 provides examples of drugs and metabolites that might be included in a pain management panel. In contrast to federally-regulated testing and the historical medical review paradigm, clinical necessity has broadened the panel of relevant analytes that must be available for testing in the pain management paradigm (which are evolving) in order to better understand the clinical picture. To meet these needs, the current application of methodologies in pain management testing routinely identify significantly more analytes than was historically the case when discrete confirmatory testing with GC/MS was used to identify individual drugs or metabolites. Pain management laboratories must keep abreast of new pharmacotherapies and drugs of abuse as they are introduced.

To get the most out of a UDT report, clinicians ordering a test should provide sufficient information to the laboratory about the patient's current prescribed medications, including both OTC and herbal preparations, in order to receive relevant laboratory interpretation based on drugs/metabolites expected to be identified. For example, a UDT that is negative for oxycodone might be completely appropriate in the context of a preemployment drug test, but becomes a potentially "abnormal" result if the laboratory knows that this drug is being prescribed to the patient. Clinicians should also provide information about drugs that might be of particular concern. For example, if there is a known past history of fentanyl abuse by the donor, alerting the laboratory to look for fentanyl or its metabolite norfentanyl may be clinically very useful.

To get the most out of a UDT report, clinicians ordering a test should provide sufficient information to the laboratory about the patient's current prescribed medications, including both OTC and herbal preparations, in order to receive relevant laboratory interpretation based on drugs/metabolites expected to be identified.

UDT reports are provided in a variety of formats, but the elements that a laboratory may include in a UDT report are shown in Table 2. The level of "information" output from the laboratory is dependent on the input from the clinician. In general terms, a good laboratory report will contain a clear statement of drugs tested for and the cutoff concentrations or LOD used to report positive and negative results. In addition, where appropriate, there should be a basic comment as to "possible" interpretations of these results. A typical example would be the presence of oxymorphone in a patient who has been prescribed oxycodone. The laboratory should comment on the possibility that this may represent a primary metabolite of oxycodone rather than use of an unprescribed analgesic such as Opana® (oxymorphone hydrochloride).

Table 2. Elements generally included in a UDT laboratory report

Element	Details
Drugs prescribed for the patient	(If supplied by the physician)[a]
Prescription/legal drugs included in the testing[b]	Cutoff concentrations[c]
	Metabolites that are also included in the testing
Illicit/illegal substances included in the testing[b]	Cutoff concentrations[c]
	Metabolites that are also included in the testing
Specimen validity testing	Parameters included
Methods employed in the testing	Techniques (immunoassay or chromatographic [eg, GC/MS or LC-MS/MS])[c]
	Normalization*
Test commentary/ interpretation	Drugs/substances found (concentrations)
	Did testing include the listed prescribed drugs?
	Identification of prescription drugs not prescribed
	Identification of illicit substances found
	Statement regarding whether the results are consistent or inconsistent with the patient's prescribed medications

[a] The authors strongly suggest, at a minimum, providing the laboratory with details of current medications in order to obtain the most clinically relevant interpretation from any laboratory

[b] It is important to alert the laboratory to any specific concerns you might have about a particular test sample, ie, possible relapse back to misuse of a discontinued therapeutic agent or illicit substance

[c] Reporting cutoffs and testing methodologies actually used allow the ordering clinician to better interpret UDT results, especially where the apparent absence of an expected drug is being questioned

Table 3. Approximate windows of detection of drug in urine

Drug	General detection time in urine[a]
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 – Benzoylecgonine after cocaine use	Hours – 2 to 4 days
Opiates (morphine, codeine) – Heroin (diacetylmorphine) – 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 the specific agent and quantity used)	Days to weeks

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

[a] The detection time of drugs formulated into extended-release or transdermal dosage formulations may be longer

Table 4. Normal characteristics of a urine specimen[35;37]

Temperature within 4 minutes of voiding	90°F to 100°F[a] (32°C to 38°C)
pH	4.5 to 8.0[b]
Urinary creatinine	>20 mg/dL (>2 mol/L)
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[38]

A laboratory report which attempts to compare observed drug concentrations to some arbitrary population of reference users to demonstrate adherence or nonadherence is, in the authors' opinion, unwise. At best, this information can easily be misinterpreted, leading to inappropriate clinical decisions. At worst, this information may be used in a medico-legal context to challenge the judgment of the clinician.

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.[32] Although governed by various factors, including dose, route of administration, metabolism, fat solubility, urine concentration (dilute versus concentrated), and pH, the detection time of most drugs in urine is 1 to 3 days **(Table 3)**.[33;34] This makes urine an effective matrix for drug testing. Long-term use of lipid-soluble drugs such as marijuana, diazepam, ketamine, or phencyclidine (PCP) may extend the window of detection to a week or more. Use of extended-release or transdermal dosage forms may also extend a drug's window of detection beyond 3 days. 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†—identifying cocaine in a urine specimen indicates either very recent use or inadvertent 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 4)**.[14;35-38] The color of a urine specimen is related to the concentration of its constituents. 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 with fluid. Concentrated urine samples are generally more reliable than dilute samples. In the absence of underlying renal pathology, patients who repeatedly provide dilute urine samples (ie, random urinary creatinine <20 mg/dL or specific gravity <1.003) 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, making a highly dilute sample more suspect.

* Normalization: a method utilizing urine specific gravity or creatinine concentrations to remove hydration effects, allowing UDT results to be compared; eg, serial UDT analyte trends

† Benzoylecgonine, a metabolite of cocaine, may be abbreviated to BZE or BEG

Specimen Collection

Because UDT in the clinical context is used to enhance patient care, the vast majority of patients are not going to tamper with their urine samples, and so a witnessed sample collection is rarely indicated.[3;10] However, certain things can be done to improve the reliability of the results obtained, including attention to the temperature and volume of the sample, and visual inspection of the sample color.[8] 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. Because laboratories keep specimens for a variable period of time, check with the laboratory before testing to determine how long negative and positive samples are stored for and their availability for additional testing, should this be required.

CURRENT USES OF URINE DRUG TESTING

Although forensic UDT remains the most common use of UDT in the United States, it should not be routinely performed by primary care clinicians. It will be briefly described here in order to inform clinicians 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 include marijuana, cocaine, opiates, PCP, and amphetamines/methamphetamines.[14;37;39] In addition, since 2010, the Mandatory Guidelines for Federal Workplace Drug Testing Programs have incorporated tests for a broader range of illicit substances, including the expanded "designer" amphetamine class:[37]

- 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy," "Adam," or "Molly")
- 3,4-methylenedioxyamphetamine (MDA or "Love Drug")
- 3,4-methylenedioxyethylamphetamine (MDEA or "Eve")

The Department of Health and Human Services (HHS) is currently updating the Mandatory Guidelines for Federal Workplace testing, which are expected to include the semisynthetic opioids oxycodone, oxymorphone, hydrocodone, and hydromorphone because of their widespread abuse.[40;41] It is also anticipated that oral fluid will become an accepted alternative specimen permitted under the Mandatory Guidelines.[40;41]

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.[14] In the federal model, positive results must be confirmed by a more specific method such as GC/MS or LC/MS.[37;42] The cost associated with the split sample and chain of custody requirements for federally regulated testing are not necessary to incur in clinical practice.[3] **Table 5** shows the current federally mandated immunoassay screening and confirmation cutoff concentrations for drugs included in federally regulated testing.[42] 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 where a cutoff of 2000 mg/mL is acceptable due to the largely negative donor population, are typically too high to be used clinically. While the entire forensic testing paradigm is of limited use in clinical care, it does set a standard for analytical quality and precision measurement.

Table 5. Initial and confirmatory cutoff concentrations[a] used for federally regulated testing[37;42]

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	Benzoylecgonine	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; 6-MAM=6-monoacetylmorphine; PCP=phencyclidine; MDMA=3,4-methylenedioxymethamphetamine; MDA=3,4-methylenedioxyamphetamine; MDEA=3,4-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 cutoff 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

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.[9;10;43;44] Such nonregulated testing may utilize a chain of custody, split samples, and secure storage of non-negative test specimens.[43] 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, such as oxycodone, oxymorphone, hydrocodone, hydromorphone, methadone, buprenorphine, benzodiazepines, and barbiturates, with more being added continually.[8;14]

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.[45] 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.[6] However, many laboratories now specialize in pain management testing with a panel of analytes that is optimized for clinical use.[30] When used with an appropriate level of understanding, UDT may 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.[2;3;6;11;45-47] 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 complex clinical picture, or has experienced trauma).[6;7;10] Chemical dependency programs regularly perform UDT to monitor patients' adherence to maintenance drugs, to reinforce healthy behavioral change, and to assist in further treatment.[6;10] Other examples of clinical uses include testing prior to certain medical procedures and testing pregnant women to help identify, where it exists, substance misuse or addiction.[6;10;48]

The remainder of this monograph will focus on the use of UDT used to assist in monitoring adherence to a controlled substance treatment regimen (eg, for chronic pain, including palliative care). Although there is no scientific evidence to support the notion that quantitative UDT provides more information than qualitative UDT with respect to determining adherence with specific dosing recommendations or to identify drug misuse or addiction, it is often the only way to determine if an analyte pattern represents an expected metabolite of a legitimately prescribed medication or the unsanctioned use of another, unprescribed agent.[1-3;10;46;49-51] Quantitative UDT can be useful in other ways, such as differentiating between primary analytes and secondary analytes (ie, metabolites) or in comparing serial patient results in tapers. Just as clinicians use hemoglobin A1c to monitor glycemic control and as an objective measure of diabetes treatment effect, they can use discordant UDT results to motivate patient change and to guide ongoing treatment, especially where agents that have abuse potential are used.[49] Testing cannot, however, substitute for diagnostic skills or an ongoing therapeutic alliance with a patient.[33] Over reliance on drug testing without good clinical judgment—particularly for contested results—can increase the focus on the test at the expense of the therapeutic relationship with the patient.[52]

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UDT, however, is generally underutilized in clinical practice, both in primary care and specialty practices:

- 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.[53]
- A 2006 to 2011 study of a cohort of Medicare patients prescribed extended-release oxycodone found that at least one UDT was billed in only 14% of cases, although the frequency of UDT did increase from 9% in 2006 to 19% in 2011.[54]
- 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.[55]
- Following institution of an intake assessment for risk of problematic medication use that included a provision for UDT, a chart review of new patients in a pain management center still found that only 19% had a urine sample submitted for testing.[56]
- A retrospective review of medical records of patients who had filled at least 6 prescriptions for opioid medications over a 1-year period in primary care clinics associated with a large VA medical center found that only 15% included documentation of UDT, despite this being recommended in VA chronic pain management guidelines.[57]
- A retrospective review of medical records of pain patients seen in an outpatient palliative care clinic over a 6-month period found that only 4% of visits included UDT.[58] However, when utilized, 56% of UDT results were aberrant (negative for prescribed opioids, positive for nonprescribed drugs, or positive for illicit drugs).[58]

The appropriate use of UDT as one of several medical management tools (eg, treatment agreements, pain scales, pill counts, querying state prescription monitoring programs [PMPs]) can help clinicians manage prescribing of controlled substances by improving adherence monitoring and offering greater protection from drug misuse and diversion.[1;2;4;50] However, it should be noted that a systematic review by the Agency for Healthcare Research and Quality found that there were

no studies that evaluated and demonstrated the long-term effectiveness of such risk mitigation strategies, including UDT, on clinical outcomes related to overdose, addiction, abuse, or misuse.[59] Nevertheless, use of such tools may help overcome a major barrier to effective pain relief—clinicians' fear of addiction or relapse of previously addicted patients.[60] However, while some clinicians may feel comfortable utilizing UDT in clinical care, it is important that they also recognize the pitfalls and limitations of testing, and seek advice from experts to overcome these challenges when ordering tests and interpreting results in order to prevent patient harm.[1;2;61] This is illustrated by 2 studies that assessed physicians' ability to interpret UDT using a 7-question instrument, consisting of 6, 5-option, single-best-answer multiple-choice questions and one yes/no question.[62;63] In these studies, only 20% to 30% of the respondents who used UDT in their practices were able to answer more than 50% of the questions correctly—none of the respondents correctly answered all questions.[62;63]

As well as underuse, it is also possible to overuse UDT, especially in high-risk patient populations where it might appear logical that more is better.[5] Clinicians must strike a balance between testing enough versus testing too much, both in terms of frequency of testing and what analytes to test for.[5] In a patient-centered model of care, any testing should provide information that is clinically useful.[5] To meet the basic standards of medical necessity, it is important to ask, answer, and document why the test was ordered, what results were obtained, and what changes in clinical course were made (if any) as a result of the test results.[5] However, studies show that a large proportion of clinicians are not following the last element.[64] A retrospective chart review of primary care patients with chronic noncancer pain who received opioid prescriptions for 3 or more consecutive months in a VA medical center found that when patients had a UDT result that was positive for illicit drugs or unreported opioids or that was negative for the prescribed opioids, only 28% of patient charts had any documentation of discussion with the patient or discontinuation of their opioid therapy by the prescriber.[64] In the majority of cases, the current opioid prescriptions were continued as usual.[64] While there are often a variety of "correct" options to take in these cases, there is arguably one clearly "wrong" answer: to do nothing.

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Some studies have shown that clinicians use UDT results to discharge patients from their practice rather than taking corrective action, such as counseling, interval dosing, limiting the quantity of the drug prescribed, conducting psychological and/or addiction evaluations, and/or discontinuing the medication.[65] A survey of members of the Texas Pain Society found that 20% would discharge a patient if prescribed drugs were not detected by UDT, 25% would discharge the patient if nonprescribed prescription drugs were detected, and 45% would discharge a patient if illicit substances were detected.[65] A total of 49% of respondents had discharged more than 10 patients in the previous year for UDT violations or irregularities.[65] The majority of respondents (60%) were not at all hesitant to dismiss UDT violators.[65] One would hope that UDT results were not the sole consideration in the dismissal of these patients.

Unexpected UDT results are an opportunity to initiate a dialogue with the patient about the meaning of these results.[3;5] The patient can chose to acknowledge the result and explain the circumstances surrounding it to the clinician (a healthy choice) or they can deny it (an unhealthy choice).[5] It is then the responsibility of the clinician to document the result, the ensuing discussion with the patient, and any actions subsequently taken (eg, tightening of boundaries or discontinuing the prescribing of controlled substances).[3;5] In some cases, the reasonable course of action to take may be to discontinue prescribing the controlled substance, but it is important to convey to the patient that "firing the molecule" is significantly different than firing the patient.[5]

IMPROVING RELIABILITY OF PATIENT-CENTERED CLINICAL TESTING

The clinical value of UDT depends on the clinician understanding the strengths and weaknesses 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, clinical pharmacist, 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;6;9;66] 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 and supplements, and document the time of their last use.[30;67;68]

Clinicians should advise the testing laboratory if the presence of any particular substance or group of substances is suspected or expected.[3;9] 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.[14;69] 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).[69] In the clinical setting it is important that 300 ng/mL or less be used for initial

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screening of opiates (most pain management laboratories typically use cutoffs much lower than this).[30] 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), laboratory-based specific drug identification of opioids should be at the laboratory's limit of detection and not some arbitrary threshold valule. 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 panels specifically for use in the pain management setting, some of which can be tailored to a particular practice's needs, 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 current federal program*, although they may be contributing to a positive opiate class 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 at any level by current opiate class immunoassays (or by those currently under consideration for use in the federal program). A positive immunoassay opiate screen in the context of these prescribed opioids necessitates more specific identification of the substance(s) that account for the positive result.

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. Unfortunately, all laboratories are not equal, and a call to the laboratory director or toxicologist may help to determine that laboratory's analytical capabilities. It is only by discussing your clinical needs with the laboratory that you can help to ensure that your testing needs will be met, especially around reporting positive results down to the LOD. As the field of pain management testing continues to grow, one would expect laboratories to have a credible internal system of checks and balances in place to ensure accuracy of their reported results, and that external proficiency testing will become a mainstay of credible pain management laboratories.

Issues for clinicians to address when initially evaluating a laboratory include:

- Ability to talk to technical staff at the lab about specific tests or results
- Cutoff concentrations and LOD reporting
- Turnaround time and methods that the lab uses to report and deliver test results
- Sample storage times for both positive and negative samples
- Drugs/metabolites offered by the lab and the ability to customize these according to patient needs
- The internal protocol for a quality assurance program (eg, blinded specimens in each/some runs)

WHY TO TEST

Why to Test
Advocate for patients
Identify use of illicit or nonprescribed drugs
As part of "Universal Precautions"
Suspected diversion

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 deemed otherwise medically necessary.[1;2;46;51;67] UDT can help patients struggling with problematic drug use to adopt or maintain healthy lifestyle changes, or to initiate a dialogue with their clinician regarding such behavior that may not yet have become problematic.[5]

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 level of risk for aberrant drug-related behaviors.[1;2] 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.[49;51] However, following a minimum statutory requirement may not be medically sufficient to meet clinical requirements in all cases. Unfortunately, it is equally possible that state or federal regulations may require UDT that is not, in the strictest sense, medically necessary. What impact, if any, that this might have on reimbursements is unclear at this time. If the patient is displaying aberrant behavior, testing frequency should be sufficient to assist in documenting the efficacy of an 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 results 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.[3;70-72] 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 many patients with chronic illnesses, including chronic pain. The treatment agreement should be readable, reasonable, and flexible.[73] The fact that the patient and clinician have agreed to UDT 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**.

* The opioids included in the federal program are currently under review—it is expected that hydrocodone, hydromorphone, oxycodone, and oxymorphone will be added.[40]

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 may limit the options that I can safely offer you in terms of medication management."
Example 2: Existing patient[a]	
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, and I fully support this."

[a] 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 help manage risk, in lieu of formal participation in the UDT process

Advocate for Patients

Clinicians can use UDT as an objective tool to assist in credible patient advocacy, for example in family and workplace situations. UDT is only one of many clinical tools that are important to assess patient adherence to the agreed-upon treatment plan and to help assess patient stability.[46] 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 document patient stability in such situations.

Identify Use of Illicit or Nonprescribed Licit Drugs

UDT can aid the clinician 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 adopting more appropriate behavior; 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 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).[2;3;45;46;74;75] 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 more careful use of a treatment plan.[45]

Table 6. The 10 principles of Universal Precautions[45;76]

1. Make a diagnosis with appropriate differential and a plan for further evaluation and investigation of underlying conditions to try to address the medical condition that is responsible for the pain
2. Psychologic assessment, including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Pre-/post-treatment assessment of pain level and function
6. Appropriate trial of opioid therapy +/- adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the "Four As" of pain medicine[a] • **A**nalgesia, **A**ctivity, **A**dverse reactions, and **A**berrant 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.

Table 7. Triage of the chronic pain patient within the Universal Precautions paradigm[45;76]

Group I: Primary care patients
This group has no past or current history of substance-use disorders. They have a noncontributory family history with respect to substance-use disorders and lack major or untreated psychopathology. This group clearly represents the majority of patients who will present to the average primary care practitioner.
Group II: Primary care patients with specialist support
In this group, patients may have a past history of a treated substance-use disorder or a significant family history of problematic drug use. They also may have a past or concurrent psychiatric disorder. These patients, however, are not actively addicted but do represent increased risk that may be managed in consultation with appropriate specialist support. This consultation may be formal and ongoing (comanaged) or simply with the option for referral back for reassessment should the need arise.
Group III: Specialty pain management
This group of patients represents the most complex cases to manage because of an active substance-use disorder or major, untreated psychopathology. These patients are actively addicted and pose significant risk both to themselves and to the practitioners who often lack the resources or experience to manage them. The prescription of controlled substances should generally be left to those persons with the experience and resources to manage the patient with an active substance-use disorder.

Gourlay DL, Heit HA, et al. *Pain Med.* 2005;6:107-112.
Gourlay DL, Heit HA. *Pain Med.* 2009;10(suppl 2):S115-S123.

* 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.

Universal Precautions

A "Universal Precautions"* approach to the assessment and ongoing management of chronic pain patients recommends 10 principles **(Table 6)** and a triage scheme **(Table 7)** for stratifying risk that includes recommendations for management and referral.[45;76] 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;[2] a review describing the benefits and limitations of several such tools was published by Passik and colleagues in the journal *Pain Medicine*.[77] These tools may be of some use 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 and the necessary time is taken to begin to know the patient on a more personal level. Until then, a presumed or initial risk should be used. Because risk is dynamic, it should be reassessed periodically over time as more information becomes available. An apparently "low-risk" patient who is found to have used cocaine should no longer be reasonably seen as low risk, even if they agree to no longer use such illicit substances.

Suspected Diversion

Diversion is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale, distribution, or use.[47] UDT cannot identify diversion, which is much more complex than the simple 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 of the prescribed controlled substance early, and multiple other factors (eg, cessation or change of insurance coverage, monetary difficulties).[46] This needs to be addressed in a patient-centered context.[46;49] One should always discuss unexpected results with the patient to determine the "motive" behind the possible aberrant behavior.[76]

In addition, quantitative assessment of a drug analyte in urine does not provide reliable evidence of diversion. At best, it also opens up a broad differential, such as bingeing, running out of the medication due to lack of insurance, or not being able to afford the medication.

When examining whether a patient is taking the prescribed medications, it is essential to know the characteristics of the test being ordered, such as the ability to detect certain drugs. Also be aware of the 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.

WHOM TO TEST

Whom to Test
New patients already receiving a controlled substance
Patients who are resistant to full evaluation
Patients who request a specific drug
Patients who display aberrant behavior
Patients in recovery
Special populations (palliative care, obstetrics)

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 referral to specialty care. 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, self-report of multiple drug intolerances and allergies, frequent telephone calls) may miss a significant number of those individuals using unprescribed or illicit drugs.[78;79] 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.[12;46;51;66;78-81] Likewise, the appearance, ethnicity, language, or culture of a patient are not reliable indicators of risk of aberrant drug-related behavior; a rational protocol of performing UDT that includes all patients receiving or being considered for prescription of controlled substances can help to validate and destigmatize patients. Because risk is ubiquitous, the question must not be "Is there risk?"—if you have a pulse, you have risk.[5] The real question is, "What is the risk?"—low, medium, or high—and more importantly, "How can that risk be best managed?"[5]

Because risk is ubiquitous, the question must not be "Is there risk?"—if you have a pulse, you have risk. The real question is, "What is the risk?"—low, medium, or high—and more importantly, "How can that risk be best managed?"

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. Detection of the drug and/or metabolite 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 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 substance-use 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 general 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

* Universal Precautions in pain management: recommendations to guide patient assessment, management, and referral in order to improve patient care, reduce stigma, and contain risk[45;76]

controlled substances after they have appropriately assessed and evaluated the clinical situation.[76] In the authors' opinion, prescribing controlled substances to patients who are "philosophically opposed" to UDT is relatively contraindicated.[73]

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 should be a cautionary point; for example, a claim of allergy to all but one specific drug with high misuse potential is a significant 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.[82] 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).[83] 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.[3;4;80;83-85] Other such behaviors include seeking out pain medications from multiple clinicians, 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.[3;4;80;83-85] Often, however, it may be easier to identify aberrant behaviors than to understand the causes or motives behind them.[86] 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*.[85;87]

Although no single aberrant behavior is pathognomonic of misuse or addiction, such behavior should never be ignored. The diagnosis of a substance-use disorder 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 rational and effective treatment of poorly controlled pain is the hallmark of pseudoaddiction.[86] Indeed, iatrogenically driven aberrant behavior can be the result of overly proscriptive treatment agreements or excessive UDT, for example. 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. In such cases, medication dose increases and loosening of boundaries should only occur after the patient demonstrates discontinuation of cocaine use or is engaged in concurrent treatment for cocaine abuse/addiction.

Patients in Recovery

Patients who have struggled with substance-use disorders in the past 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.[51;73] 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 should also not typically be considered as agents of last resort.[73] Implementing monitoring strategies, including UDT, becomes especially important when managing patients who have substance-use histories.[51;73] Knowing that UDT is used in your practice can also help patients to make better choices.[5]

Special Populations

Palliative Care

Patients with life-limiting illnesses, including cancer, are not exempt from the problems of drug misuse, substance abuse, and addiction.[10;88;89] For example, one study diagnosed alcoholism in up to 28% of terminally ill cancer patients.[90] Clinicians can sometimes have a sense of futility about treating substance-use disorders at the end-of-life, but such disorders are treatable, which can also facilitate patient engagement and optimal treatment of pain at the end-of-life.[10;89] Therefore, UDT can be useful to identify aberrant drug-related behavior, facilitate a therapeutic discussion, and guide restructuring of treatment to optimize safety and efficacy for the patient.[10] UDT can also support recovery by helping to identify subsequent lapses or relapses, so that these can be addressed.[10]

Obstetrics

According to the 2013 National Survey on Drug Use and Health, 5.4% of pregnant women are current users of illicit drugs and 9.4% report current alcohol use.[91] Between 2000 and 2009, antepartum maternal opioid use increased from 1.19 to 5.63 per 1000 hospital births per year and the incidence of neonatal abstinence syndrome caused by maternal opioid use increased from 1.20 to 3.39 per 1000 hospital births per year.[92] Therefore, use of UDT in the obstetric population may help to identify use of illicit drugs and alcohol and provide an opportunity to educate patients and motivate, where necessary, positive behavioral change.[10]

WHEN TO TEST

When to Test
When meeting a patient for the first time
When starting treatment with a controlled substance
When making major changes in treatment
To support a decision to refer

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

When Meeting a Patient for the First Time

Substance-use disorders are not uncommon in the general population (they may be more or less common in your practice depending on your demographics), so UDT should be a familiar tool used in primary care.[49] It should be considered as a part of the evaluation of any new patient who is taking controlled substances or for whom controlled substances are being considered. Discussing UDT with all patients presenting with chronic pain can help 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 we really do not know how many patients engage in problematic opioid use (including misuse/addiction), those who do generally have a current or past history of substance misuse or addiction, or a significant family history.[93] 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 a controlled substance.[93] 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.[93]

A history of substance misuse does not preclude appropriate treatment with any medication, including a controlled substance, but it does increase risk.[2;45] When indicated (eg, opioid analgesia to relieve pain), such a history requires a treatment plan with firmly defined boundaries, as well as clearly defined endpoints of success.[2;45] Clinically, a patient in recovery from the disease of addiction can be cautiously managed by setting careful and strict boundaries, which may include random UDT, a treatment agreement, and referral to, or comanagement with, a recovery* program or someone more experienced in the management of such patients.[2;3;73] A patient with active addictive disease must engage in a program of concurrent management of his or her substance-use disorder, including a program of 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.[76]

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.[32] It must be emphasized that the controlled substance is prescribed to treat the primary pain 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 such cases, it may be wise to seek comanagement of the patient with a knowledgeable substance-use treatment professional.

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 may restrict his or her ability to do a good job in managing that patient and may limit the options available for optimal medication management.[5] The use of UDT can help clinicians convey to patients their commitment to the safe and ethical practice of pain medicine.[5] It can also demonstrate to regulatory authorities their commitment to the credible assessment and management of risk.[5]

When Making Major Changes in Treatment

Modification of therapy, particularly a 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.

To Support a Decision to Refer

The Federation of State Medical Boards' *Model Policy on the Use of Opioid Analgesics in 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).[3;72]

Unexpected positive or negative UDT results should be verified, where necessary, through discussion with the laboratory. When such UDT results cannot be clarified through discussion with the patient, they 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.[3;10;72;93] For clinicians who do not have formal referral resources available in this often underserved area of pain and addiction medicine, informal support from a more experienced colleague 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.[76] 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 underdiagnosis of substance misuse or addiction.[61] 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.[3] The testing laboratory or POC device manufacturer should provide readily accessible consultation and results interpretation in a relevant clinical context.[30;33;66]

* Recovery: a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential[216]

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.[21] For example:

- Tests for cocaine react principally with cocaine's primary metabolite, benzoylecgonine. These tests have low cross-reactivity with other substances and, therefore, a positive result is highly predictive of cocaine use.[8]
- Tests for amphetamine or methamphetamine are subject to significant cross-reactivity. The tests 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 to distinguish between chiral* forms of methamphetamine (eg, "chiral" chromatography) *(see page 17 for more details)*.
- Immunoassay testing for opiates is very responsive for morphine and codeine, but does not distinguish which is present. However, opiate immunoassays show a lower sensitivity for semisynthetic opioids and are unable to detect synthetic opioids, so even large concentrations of drug/metabolites in urine may not be reliably detected by the opiate immunoassay *(see page 18 for more details)*.[21;32;94;95] 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 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 chromatographic testing, which avoids the cross-reactivity limitations of POC and laboratory immunoassays.

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.

Table 8. Examples of potential false positives due to cross-reacting compounds for certain immunoassays

Immunoassay affected[a]	Cross-reacting drug[b]
Opiates	Quinolone antibiotics (eg, levofloxacin, ofloxacin)[96;97]
Buprenorphine	Tramadol (analgesic)[114]
Fentanyl; MDMA (Ecstasy), amphetamine	Trazodone (antidepressant)[98;102;111;116]
Benzodiazepine, LSD	Sertraline (antidepressant)[118;119]
Methadone	Quetiapine (atypical antipsychotic)[105]
Methadone	Tapentadol (analgesic)[121]
PCP	Venlafaxine (antidepressant)[100;103]
PCP	Dextromethorphan (antitussive)[108]
PCP	Tramadol (analgesic)[109;123]
PCP	Lamotrigine (anticonvulsant)[120]
Amphetamine	Selegiline (for Parkinson's disease)[99]
Amphetamine	Promethazine (for allergies, agitation, nausea, vomiting)[107]
Amphetamine	*l*-methamphetamine (over-the-counter nasal inhaler)[14]
Amphetamine	Pseudoephedrine (over-the-counter decongestant)[115]
Amphetamine	Bupropion (antidepressant)[104]
Amphetamine	Ranitidine (histamine H2-receptor antagonist)[112]
Fentanyl	Risperidone (antipsychotic)[113]
THCA, benzodiazepine	Efavirenz (antiretroviral)[101;106;122]
THCA	Proton pump inhibitors (eg, pantoprazole)[110]

LSD=lysergic acid diethylamide; MDMA=3,4-methylenedioxymethamphetamine; PCP=phencyclidine; THCA=delta-9-tetrahydrocannabinol-9-carboxylic acid

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

[b] Or metabolite of the drug

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.[96;97] 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,[98] amphetamine assays with selegiline,[99] and some PCP immunoassays with the antidepressant venlafaxine.[100] Examples of other agents that can cross-react with immunoassays are shown in Table 8.[96-123] Because testing technology is constantly

It is important to contact the laboratory when looking for a specific substance to ensure that the correct test/profile is used.

* Chiral molecules with one or more stereocenters can be enantiomers that are mirror images of one another (eg, left or right handed molecules). Enantiomers rotate plane polarized light in different directions. If enantiomers rotate the light clockwise, they are known as dextrorotatory and are denoted as *d* isomers. If the light is rotated counterclockwise they are known as levorotatory and are denoted as *l* isomers.

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 and contested 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.[33] 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.[33] There is currently ***no*** scientifically validated relationship between the concentrations reported in the urine and the doses taken of any drug.[10;66;82;124;125]

There is currently no scientifically validated relationship between the concentrations reported in the urine and the doses taken of any drug.

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.[45] Although the substance-use disorder does not diminish the patient's complaint of pain, it often complicates the management of it.

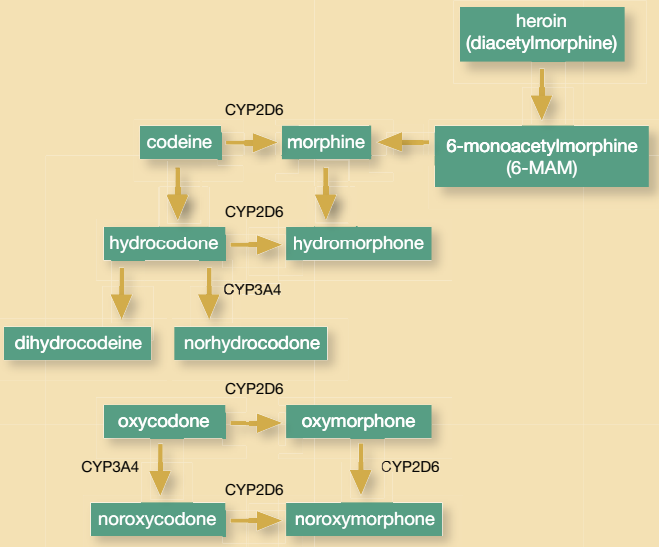
Positive Results That Are Misleading

Opiates: For patients not prescribed morphine, the presence of morphine in urine is often assumed to be indicative of heroin use.[67] However, a morphine-positive UDT may also result from codeine and from morphine in foodstuffs (eg, poppy seeds in some breads or confectioneries).[14;33;66;126;127] 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)**.[14] 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.[14;34;128] New evidence suggests that, although rare, the presence of parent heroin and 6-MAM in urine may occur in the absence of morphine.[129] The reasons for this are not yet understood and the prevalence of this finding is very low.[129]

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.[14] Clinicians should maintain a list of all prescription, OTC, and herbal products that a patient is taking while participating in a UDT surveillance program, 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.

Figure 1. Examples of metabolism of opioids, showing major cytochrome P450 enzymes involved in phase 1 metabolism



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

Clinicians should maintain a list of all prescription and OTC products that a patient is taking while participating in a UDT surveillance program.

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

Opioid metabolism: *(See Figure 1)*

- Codeine is metabolized to morphine, so both substances may occur in urine following codeine use:[14;66;67]
  - 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 (~10%),[130] but the reverse does not occur.
    - Morphine preparations may have small amounts of codeine as an impurity from manufacture (generally about 0.04%).[131]
  - Codeine alone is possible because a small proportion of patients (<10% of the Caucasian population) lack the

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

necessary activity of the cytochrome P450 (CYP) 2D6 enzymatic pathway to convert codeine to morphine.[132] Patients on certain CYP2D6-inhibiting drugs may also lack the ability to convert codeine into morphine, potentially complicating UDT interpretation, and reducing codeine effectiveness.

- Morphine may be metabolized to produce small amounts (generally <5%) of hydromorphone.[68;133-139]
- Hydrocodone may be metabolized to small quantities of hydromorphone.[140;141]
- Codeine may be metabolized to small quantities (generally <15%) of hydrocodone.[142]
- Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone.[8;143] 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 oxymorphone is a metabolite rather than a parent compound.[8] 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).[8]
  - Oxycodone preparations may have small amounts of hydrocodone as an impurity from manufacture (generally <0.01%).[144]

Cocaine: Cocaine is a topical anesthetic with limited clinical uses in certain trauma, dental, ophthalmologic, and otolaryngologic procedures.[14;145] A patient's urine may test positive for the cocaine metabolite, benzoylecgonine, after such a procedure for up to 2 to 3 days. However, a licensed health care professional must order its use, which can be checked through medical records or by contacting the treating clinician. There is no structural similarity between other topical anesthetics that include "caine" in their name (eg, prilocaine, lidocaine) and cocaine or benzoylecgonine; therefore, cross-reaction does not occur.[14] A positive chromatographic UDT result for benzoylecgonine, in the absence of a medical explanation, should be interpreted as due to direct exposure to cocaine.[8] Cocaine parent can be detected by GC/MS and similar methods only with very recent use because of its short half-life and spontaneous degradation to benzoylecgonine.

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.[99;115] 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 some OTC products (various brands of *l*-methamphetamine). Methamphetamine exists as 2 isomers that are designated *d*- and *l*-.[14] 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 normal chromatography, 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.[146] This must be specifically requested of the laboratory.

For example, the OTC Vicks® Inhaler marketed in the United States contains levmetamfetamine (*l*-desoxyephedrine also known as *l*-methamphetamine).[14] 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 levmetamfetamine.

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 test 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.[33;67] This may occur for a number of reasons, such as the patient being unable to afford the cost of the medication due to lack of insurance, noncoverage by insurance, or a high copay; running out of the drug early because of bingeing; or diverting the prescribed medication. In the context of adherence testing, this can adversely affect the therapeutic alliance; therefore, an open and frank discussion with the patient and/or consultation with the testing laboratory are indicated. Additional, specific testing of the specimen may be necessary.

Clinicians 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). However, this is not always the case. In certain cases, UDT may detect traces of unexplained opioids that are in fact metabolites **(Figure 1)**. For example, a patient who is prescribed codeine may show trace quantities of hydrocodone that may not represent hydrocodone use.[142] Detection of minor amounts of hydrocodone in urine containing a high concentration of codeine should not be interpreted as evidence of hydrocodone use.[30] In the case of a patient who is prescribed hydrocodone, quantities of hydromorphone may be detected because of hydrocodone metabolism.[140;141] 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.

* 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.

Table 9. Common 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 or in sufficient quantities to be detected
• The patient has not used the drug/medication recently or 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 tested sample was not the patient's own urine
• The patient has diverted the medication

Although it is theoretically possible to detect tertiary analytes in urine (eg, hydromorphone resulting from the metabolism of codeine to hydrocodone and then hydrocodone to hydromorphone), this is unlikely, and the clinical relevance of potential tertiary analytes remains unknown. In such cases, it is important to rely on the impressions of the laboratory for guidance as to whether this is an expected or unexpected finding.

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 9)**.[30]

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 9)**. 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.

A negative result for a prescribed medication can also be the result of patients substituting a urine sample that was not their own. Substitution of a sample is usually done for one of two reasons—to show evidence of a drug that they are prescribed but not taking, or to provide a urine that does not contain substances that they should not be taking.

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, urine, nor oral fluid drug concentrations have been clearly demonstrated to answer these questions. The drug that a patient is most able to abuse with impunity is the one that is legitimately present in urine, because it has been prescribed for the patient. 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).

Table 10. 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	

The drug that a patient is most able to abuse with impunity is the one that is legitimately present in urine, because it has been prescribed for the patient.

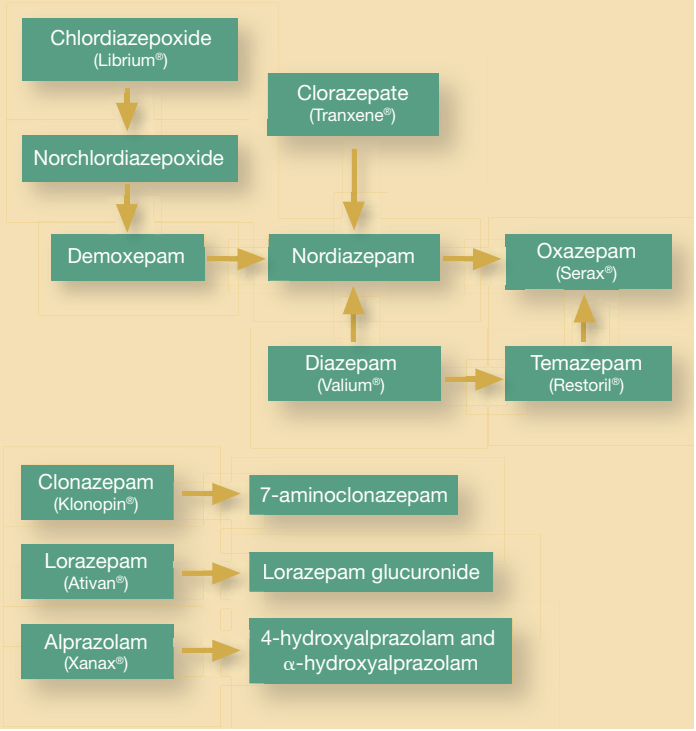
Semisynthetic Opioids: The most widely used opiate immunoassays detect morphine and codeine, but do not reliably detect semisynthetic opioids, such as oxycodone or hydromorphone **(Table 10)**, unless an immunoassay specifically directed toward these particular molecules is used.[14] It is possible that 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, most respondents were unaware that oxycodone is not reliably detected by most opiate immunoassays.[147] Only 12% of primary care physicians correctly knew that testing for oxycodone must be specifically requested when ordering UDT.[147] 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.[63]

Buprenorphine has become a more significant drug of abuse as its availability in the office-based treatment of opioid addiction has increased.[148-150] However, many laboratories do not routinely test for buprenorphine.

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 and it will depend on which molecule the immunoassay is based on. False-negative rates of 20% to 35% are not uncommon, and one study found false-negative rates of 31%, 63%, and 75% with 3 different benzodiazepine immunoassays in comparison with LC-MS/MS.[151-153] Clinicians should carefully interpret the presence or

Figure 2. Some examples of benzodiazepine pathways of metabolism



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)**. Immunoassays are insufficient to detect benzodiazepines, and even more definitive laboratory-based testing for benzodiazepines pose significant challenges, in both detection and clinical interpretation.

Concentration Effects: It is important to know the threshold concentrations that your laboratory uses when interpreting a report of "no drug present."[6;67] 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 low doses). Positive results in dilute urine are readily interpretable, but a negative result in dilute urine may be much more difficult to interpret. Laboratories are able to apply drug normalization procedures to dilute urine samples based on specific gravity or creatinine measures, and adjust concentrations (normalization) to values which allow for direct comparisons of UDT sample results within individual patients.[31] This can result in greater drug concentrations that trigger a positive result above the threshold used for a particular test.[31] If a sample is sufficiently dilute to result in an apparent negative result that is below the limit of quantitation (LOQ), the ability for any further interpretation is lost, because such a result cannot be normalized. Drug normalization can be useful when comparing serial UDT results for an individual patient, particularly when urine samples are taken at different times of day.

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 pharmacokinetic 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, even quantitative UDT cannot indicate the amount of drug taken, when the last dose was administered, the route of administration, or the source of that drug (licit or illicit).[9;66]

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 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, both within and between subjects), 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 concentrations should not be used to extrapolate backward and make specific determinations regarding the dose taken and the pattern of ingestion of the prescribed drug. Software and laboratory products making these claims have not been validated scientifically or 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.[82;125]

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").[154] 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 the subjects in this standardized population are "known to be compliant" with their medication use is fundamentally flawed from a clinical perspective. Therefore, individual patient comparisons of detected urinary drug concentrations with respect to compliance assessment are of limited clinical value and may be misleading.

MYTHS

Passive Inhalation

Passive smoke inhalation does not explain positive marijuana results at typical cutoffs (50 ng/mL), unless environmental conditions are extreme (a sealed chamber with several individuals smoking high potency cannabis, and even then positive results are likely to be rare and limited to the hours immediately post-exposure).[14;33;155] 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 use that requires further evaluation and possible treatment.

Medical Cannabinoids

Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive substance of smoked marijuana (eg, *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.[156] The synthetic cannabinoid nabilone (Cesamet®) is also approved to treat nausea and vomiting associated with cancer chemotherapy in patients who have failed to adequately respond to conventional antiemetics.[157;158] Another drug currently available in Canada and other jurisdictions is buccal Sativex® containing THC and cannabidiol (CBD) 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.[159-161]

Smoked cannabis, orally administered Marinol®, and buccal Sativex® all produce positive immunoassay and GC/MS results for the THC metabolite delta-9-tetrahydrocannabinol-9-carboxylic acid (THCA) in urine. More specific testing (eg, for tetrahydrocannabivarin [THCV]) may be able to distinguish the subtle differences between smoked cannabis and pharmaceutical THC (eg, oral Marinol®). However, Cesamet® does not trigger a positive immunoassay screen or a positive GC/MS result for THCA because it does not contain THC.[157] There have been reports of positive urine immunoassay tests for cannabinoids in patients receiving proton pump inhibitors, such as pantoprazole (Protonix®).[110] However, a more definitive chromatographic test can rule out this immunoassay cross-reactivity.

Cesamet® does not trigger a positive immunoassay screen or a positive GC/MS result for THCA because it does not contain THC.

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.[162;163] However, multiple studies have found that the THC concentrations typical in hemp products are sufficiently low to prevent a positive result.[162;163]

There have been documented cases of cocaine ingestion by drinking tea made from coca leaves.[14;164] Although such tea may be available for purchase by unknowing consumers, the product—containing cocaine and/or related metabolites—is illegal under US Drug Enforcement Administration (DEA) and Food and Drug Administration 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, a number of synthetic cannabinoid molecules such as JWH-018 and JWH-073, which were developed in basic scientific research many years ago by the scientist John W. Huffman to study cannabinoid receptors, have seen a resurgence of interest in street drug use as "designer drugs" that produce "legal highs."[165-168] These synthetic cannabinoid molecules have been used to spike herbal mixtures that are marketed as incense, such as Spice Gold, Spice Diamond, Purple Haze, K2, and Skunk, but which are smoked for marijuana-like effects.[166;168;169] The cannabinoid constituents of these herbal blends are structurally distinct from THC and, until recently, were not treated as controlled substances in most states in the United States.[168] Hence, they provided an alternative to cannabis for people trying to avoid potential legal consequences of marijuana use or for those seeking intoxication while still passing a drug test.[168] The current legal uncertainties around many of these molecules have led to challenges at both the detection and interdiction levels. The DEA took action to control these substances in Schedule I of the Controlled Substances Act via passage of the Synthetic Drug Abuse Prevention Act of 2012.[169] Because routine urine cannabinoid immunoassays do not detect synthetic cannabinoids and new compounds are continually emerging, laboratories are challenged to identify these new designer drugs.[10;170;171]

The synthetic cathinones, commonly called "bath salts," are CNS stimulants marketed under a variety of street names, such as Blue Silk, Cloud Nine, Drone, Meow Meow, and Purple Wave.[166;172] Their use has resulted in emergency department visits throughout the United States for severe agitation, sympathomimetic toxicity, and death.[166;172] The DEA exercised its emergency scheduling authority to control these synthetic cathinones as Schedule I controlled substances.[173] However synthetic cathinones enter the drug market faster than they can be restricted—by the time enough information is known about a drug to place it under temporary or permanent scheduling, replacement compounds have already been created and distributed.[174] Laboratories are currently developing more definitive methods to identify these molecules.[165;174;175] These drugs will not be detected unless assays specifically directed towards them are ordered. As local, regional, and other geographical trends are identified over time, laboratories and clinicians may reevaluate existing test profiles.

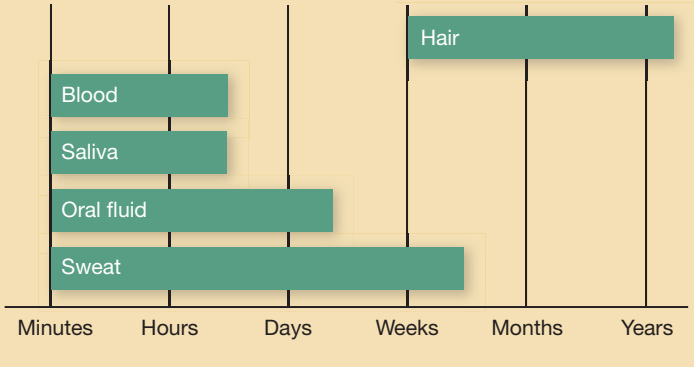
ALTERNATIVE TECHNOLOGIES FOR DRUG TESTING: BENEFITS & LIMITATIONS

ALTERNATIVE SPECIMENS

Drugs can be detected in many other biologic specimens, including blood, breath, oral fluid, hair, nails, and sweat.[176] Several specimens are commonly available as alternatives to urine for drug testing, including blood, oral fluid, and hair.[6;177] 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.[11;13;176;177]

The window of drug detection in urine, hair, oral fluid, and blood are not identical, but the results from each specimen can complement each other **(Figure 3)**.[124;177;178] 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.[179-181] Some drug classes are more difficult to detect than others for a given type of specimen.[6;178]

Figure 3. Relative detection times of drugs in biologic specimens[124]



Note: apparently overlapping detection times will not necessarily yield matching positive or negative results in all the alternate matrices

Blood/Breath

Blood testing can detect low levels of substances and is a better sample for the legal assessment of an actively intoxicated patient.[6] Although research is being conducted to correlate THC blood levels with current impairment, at the present time, alcohol is the only substance for which there is a legal relationship for blood concentration and impairment. However, some states have established THC concentration limits in blood for drivers, although there is no scientifically defined correlation between these concentrations and impairment.[182]

Blood testing is an invasive and expensive procedure, has a window of detection that is limited to current drug use, and is not amenable to rapid screening procedures.[177] Breath alcohol concentrations are strongly correlated with blood alcohol levels, and there is a well-defined and legally acceptable relationship between blood and breath alcohol levels. However, most other drugs are not sufficiently volatile to effectively use breath levels as a surrogate of drug concentrations in blood and current impairment. The increased use of marijuana, both recreationally and medically, is driving research into the use of breath collection devices.[183;184]

Oral Fluid

Oral fluid testing is increasing in popularity because it overcomes some of the problems of urine, including accessible collection in almost any location, less embarrassment, direct observation during collection to increase the sample reliability, and limited invasiveness.[26;177;179;185-187] The HHS is currently considering updating the Mandatory Guidelines for Federal Workplace Testing to allow oral fluid to become an accepted alternative specimen for testing.[40;41] 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.[177;188] 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.[189-191]

Oral fluid is composed of saliva, mixed with buccal and mucosal transudates, cellular debris, bacteria, and residue of smoked or orally ingested products.[179] 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.[179] Thus drugs are detected earlier in saliva than in urine, but for shorter time periods.[26] Oral fluid is generally useful for detecting drugs for up to 4 hours, but some drugs can be detected for up to 24 hours or more.[177;178] It is particularly amenable to post-accident testing.

Collection procedures are not standardized and can affect drug concentrations.[26] Specimens are collected by having the donor 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.[26;179;192] The sample volume of saliva necessary for laboratory testing may be difficult to obtain (eg, in individuals who are dehydrated or patients who are taking medications which promote dry mouth, although dehydration does not affect the reliability of the sample), and considerably lower drug concentrations compared with urine present an analytical challenge.[26]

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.[26;179] 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.[26;179;192]

Hair

The disposition of drugs in the body includes incorporation into growing hair, although not all drugs are equally incorporated into the hair matrix (basic drugs such as cocaine and amphetamines are incorporated at higher rates than neutral drugs [steroids, benzodiazepines, cannabinoids] or acidic drugs).[193;194] Hair may be useful to objectively document past drug use, but it is usually inefficient for clinical testing.[177;193] Testing hair can extend the window of detection for a drug to weeks or months depending on the length of the hair tested.[177;178;195;196] 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.[13;66;176;196] In fact, segmental hair analysis has recently come under judicial scrutiny. The Motherisk program at the Hospital for Sick Children in Toronto, Canada, which relied heavily on hair segment analysis in providing evidence in both criminal and civil settings, has recently been closed following an internal investigation which "further explored and validated" previous, and as yet undisclosed, "questions and concerns" about the validity of these tests.[197] While interest in hair, as an alternative testing matrix remains high, its ultimate role in both clinical and forensic settings remains to be determined.

Several mechanisms for incorporation of drugs into hair have been proposed.[193] Drugs can diffuse from arterioles within the root into the 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.[180;193;196] The ability of hair testing to distinguish drug use from external contamination (eg, drugs in smoke or the environment) remains controversial.[176;193] Measuring metabolites and washing hair samples can help prevent false-positive results from external contamination.[193;196] However, standardized wash procedures that will effectively remove any trace of external contamination without actively removing the drugs incorporated into the hair are not currently available, although several approaches have been described.[196]

There have been a number of cases where hair analysis of toddlers and young children have detected environmental exposure to drugs of abuse; either following exposure to smoked drugs or to their manufacture in clandestine laboratories.[198-200] In cases where the hair samples were washed prior to testing in order to exclude external contamination, the positive results were thought to be due to passive smoke inhalation of abused drugs, which are then incorporated into the hair through the blood stream.[198;200]

Darkly pigmented hair with a high melanin content 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 bias.[13;66;67;176;177;201] Other disadvantages of hair analysis to validate drug use include irregular growth, labor-intensive sample preparation, low analyte concentrations, and excessive cost.[13;67;176] 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.[176;196] However, methods for evading UDT do not affect hair analysis, and collection of head hair—the preferred sample—can be performed under close supervision with less embarrassment than observed urine collection, and hair does not require refrigeration and can be stored indefinitely.[195;196]

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.[185] Different biologic matrices have different cutoff concentrations for various drugs, but criteria for specimen validity have yet to be defined.[178] At present, much of the available knowledge on drug disposition in biologic matrices has been generated from single- or multiple-dosing studies, but information is limited in chronic users.[179] 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.[179] Oral fluid is promising and may be a valuable complement to UDT in clinical pain management settings.[202]

Owing to the nature of the various matrices available, it is expected that an individual may be positive in one matrix while negative in one or more of the other matrices available. For example, if a donor has urine, blood, oral fluid, and hair samples collected and submitted for testing on the same day, while there may be overlapping results between blood and oral fluid, urine may or may not be positive, and hair may or may not be positive depending on the degree and time of use. As with any laboratory test, over reliance on or interpretation of data obtained through the use of these alternate matrices may result in significant harm to the donor and/or those who have incorrectly relied upon this information.

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 markers of alcohol use that can persist in body fluids for a longer period than alcohol itself.[203-209] Although present in all body fluids and tissues, EtG and EtS are usually measured in urine, where they remain detectable for 1 to 3 days.[209] Thus EtG or EtS are highly sensitive direct biomarkers to detect alcohol use or exposure, and tests to detect these substances are commercially available. EtG and EtS test results can be used as a diagnostic aid to screen for alcohol problems, to motivate a change in drinking behavior (to abstinence), and to identify relapse to drinking.[209] 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 (typically no more than 0.5% alcohol by volume), and food stuffs. Significantly elevated EtG concentrations can also result from exposure to alcohol vapors in cleaning products and from hand washing with common hand disinfectants and hand sanitizers (eg, Purell®, 62% ethyl alcohol).[209-212] Such incidental exposure can lead to a positive EtG or EtS test result even when alcoholic beverages were not consumed, because of the high sensitivity of these tests.[209] Positive test results from extraneous exposures when alcohol beverages are not consumed can be detrimental in medical and forensic settings; clinicians should use such tests with caution only as a diagnostic aid in the total management of the patient and carefully evaluate test results and potential exposures to alcohol.[209] One strategy to help minimize this problem is to use a treatment agreement that stipulates that individuals for whom abstinence is required avoid using products that may result in a positive test, such as alcohol-based mouthwash, hand sanitizers, and hygiene products.[209]

Recent research has aimed to identify the degree to which extraneous exposures and conditions affect EtG levels to determine how EtG can be used successfully to indicate intentional alcohol use.[209] In addition, more research is needed on how the test results may be influenced by various diseases, ethnicity, gender, genetic variation in enzyme systems, or the use of drugs.[209]

There are no established cutoffs for EtG, and various laboratories may offer different interpretations.[203] Generally, EtG concentrations below 100 ng/mL indicate total abstinence from alcohol, including the elimination of all incidental exposures. Although further research is needed before firm cutoffs for EtG can be established that clearly distinguish the consumption of alcoholic beverages from alcohol in environmental products, sufficient research has been completed to reach the following conclusions:[209]

- A "high" positive (eg, >1,000 ng/mL) may indicate:
  - Heavy drinking on the same day or previously (eg, past 1 to 2 days).
  - Light drinking the same day.
- A "low" positive (eg, 500-1,000 ng/mL) may indicate:
  - Previous heavy drinking (eg, past 1 to 3 days).
  - Recent light drinking (eg, past 24 hours).
  - Recent intense "extraneous exposure" (eg, within 24 hours or less).
- A "very low" positive (100-500 ng/mL) may indicate:
  - Previous heavy drinking (eg, past 1 to 3 days).
  - Previous light drinking (eg, past 12 to 36 hours).
  - Recent "extraneous" exposure.

PHARMACOGENETICS

Pharmacogenetics may help to explain some of the variability in response to opioids that is seen in clinical practice.[213] One hopeful role for these tests may be to help predict more effective therapeutic regimens with fewer side effects. While UDT can hint at genetic issues

Table 11. Codeine phenotypes based on CYP2D6 genotypes[214]

Likely phenotype[a]	Activity score	Genotypes	Implications for codeine metabolism
Ultra rapid metabolizer (~1-2% of patients)	>2.0	An individual carrying >2 copies of functional alleles	Increased formation of morphine following codeine administration, leading to higher risk of toxicity
Extensive metabolizer (~77-92% of patients)	1.0-2.0	An individual carrying 2 alleles encoding full or reduced function or 1 full function allele together with either 1 nonfunctional or 1 reduced-function allele	Normal morphine formation
Intermediate metabolizer (~2-11% of patients)	0.5	An individual carrying 1 reduced and 1 nonfunctional allele	Reduced morphine formation
Poor metabolizer (~5-10% of patients)	0	An individual carrying no functional alleles	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief

[a] The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities

regarding opioid metabolism, for example the absence of urinary morphine in a codeine user complaining of inadequate analgesic effect, DNA testing can actually determine if the individual is or is not a CYP2D6 poor metabolizer.[213] The clinical utility and cost-effectiveness of routine genetic testing are, however, still being debated.[213]

Pharmacogenetics may help to explain some of the variability in response to opioids that is seen in clinical practice.

Pharmacogenetics describes the influence of polymorphic genes on both drug pharmacokinetics (a patient's ability to metabolize certain drugs) and pharmacodynamics (a patient's ability to respond to a drug at the level of the drug target or receptor).[213] Polymorphic genes that encode the drug-metabolizing enzymes, drug transporters, drug receptors, and other proteins can serve as markers that may help to predict the efficacy of and adverse responses to some drugs.[213;214]

One of the best characterized genes involved in the pharmacokinetics of opioids is CYP2D6 and its effect on the activity of codeine (Table 11).[213;214] Codeine, which is a prodrug, is metabolized to its active metabolite morphine by the action of CYP2D6, which plays an important role in codeine's analgesic activity.[213;214] Pharmacokinetic and pharmacodynamic studies show a decrease in morphine levels and a decrease in analgesia in poor metabolizers receiving codeine, compared with extensive metabolizers.[215] In contrast, increased conversion to morphine in CYP2D6 ultra rapid metabolizers provides, at the least, a theoretical risk of toxic systemic concentrations of morphine even at relatively low codeine doses.[215] Only time will tell if the peer-reviewed literature can document the clinical significance of this potentiality.

The field of pharmacogenetics is a rapidly expanding discipline. It holds great promise for the development of more effective therapeutic agents with fewer adverse effects, as well as allowing the clinician to potentially tailor drug regimens on an individual, genetically directed basis. However, the immediate clinical utility of this technology remains to be seen.

CONCLUSIONS

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

- Will be, or are being, treated over the long term with controlled substances, including opioids for chronic pain
- Are at increased risk for substance-use disorders
- Have other relevant medical conditions or diagnoses

Because substance-use disorders are not uncommon, UDT should be considered a core clinical tool in primary care as part of a comprehensive risk management strategy. The clinician can use UDT to help motivate patient behavioral changes and maintain healthy changes that have already been made. However, testing without an appropriate strategy for interpreting results can do significant 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 trust and honesty 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 change, if any, that results. Anomalous and unexpected results should never be ignored, and ultimately the weight placed on them will be a function of appropriate clinical interpretation.

UDT is something we should do ***for our patients*** rather than something that is done ***to them***.[5]

Complete the Online Post Test, Evaluation, and Credit Application form at www.udtmonograph6.com/credit.html

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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

Contested results: For the purposes of this monograph, a contested result is one where the patient disagrees with the UDT report/interpretation

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

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

Limit of detection (LOD): The 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

Limit of quantitation (LOQ): The minimum concentration that can be quantified at a specified level of precision or accuracy

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

Liquid chromatography-tandem mass spectrometry (LC-MS/MS): A method where a sample mixture is first separated by liquid chromatography before being ionized and characterized by mass-to-charge ratio and relative abundance using 2 mass spectrometers in series

Normalization: A method utilizing urine specific gravity or creatinine concentrations to remove hydration effects, allowing UDT results to be compared; eg, serial UDT analyte trends

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 opioid receptors

Pharmacogenetics: Describes the genetic influence on drug pharmacokinetics (a patient's ability to metabolize certain drugs) and pharmacodynamics (a patient's ability to respond to a drug at the level of the drug target or receptor)

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

Prescription monitoring program: State run programs that collect information on dispensed controlled substances into a database that can be queried by clinicians to obtain a history of controlled substance prescriptions dispensed for a particular patient

Proficiency testing: An external method of oversight, with comparative testing between laboratories that serve as a quality assurance tool. It utilizes biological specimens to which specific concentrations of relevant analytes have been added and verified by reference laboratories or participant means.

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

Qualitative testing: Determines if a particular analyte is present in a sample above a predetermined cutoff concentration

Quantitative testing: Determines the concentration of a particular analyte in a sample

Recovery: A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential

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 in order to improve patient care, reduce stigma, and contain risk

ABBREVIATIONS

6-MAM	6-monoacetylmorphine
AIDS	acquired immune deficiency syndrome
AAPM	American Academy of Pain Medicine
APS	American Pain Society
BEG	benzoylecgonine
BZE	benzoylecgonine
CBD	cannabidiol
CNS	central nervous system
CYP	cytochrome P450
DEA	Drug Enforcement Administration
DoD	Department of Defense
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMR	electronic medical records
EtG	ethyl glucuronide
EtS	ethyl sulfate
GC/MS	gas chromatography/mass spectrometry
HHS	Department of Health and Human Services
LC/MS	liquid chromatography/mass spectrometry
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOD	limit of detection
LOQ	limit of quantitation
LSD	Lysergic acid diethylamide
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	delta-9-tetrahydrocannabinol
THCA	delta-9-tetrahydrocannabinol-9-carboxylic acid
THCV	tetrahydrocannabivarin
UDT	urine drug testing
VA	Department of Veterans Affairs