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Review: Rational Use and Interpretation of Urine Drug Testing in Chronic Opioid Therapy

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Abstract. Urine drug testing (UDT) has become an essential feature of pain management, as physicians seek to verify adherence to prescribed opioid regimens and to detect the use of illicit or unauthorized licit drugs. Results of urine drug tests have important consequences in regard to therapeutic decisions and the trust between physician and patient. However, reliance on UDT to confirm adherence can be problematic if the results are not interpreted correctly, and evidence suggests that many physicians lack an adequate understanding of the complexities of UDT and the factors that can affect test results. These factors include metabolic conversion between drugs, genetic variations in drug metabolism, the sensitivity and specificity of the analytical method for a particular drug or metabolite, and the effects of intentional and unintentional interferants. In this review, we focus on the technical features and limitations of analytical methods used for detecting drugs or their metabolites in urine, the statistical constructs that are pertinent to ordering UDT and interpreting test results, and the application of these concepts to the clinical monitoring of patients maintained on chronic opioid therapy.

Keywords: morphine, codeine, hydrocodone, oxycodone, oxycontin, heroin, opiates, urine drug testing

Introduction

Chronic pain affects one third of the US population and is a leading reason for physician visits [1,2]. While a large and ever-expanding array of therapeutic options is available to treat chronic pain, the choices are often ineffective, produce unacceptable side effects, are contraindicated, or are not covered by third party payers. As a consequence, opioid analgesics are, and will likely remain, a cornerstone in the management of moderate to severe chronic pain. Opioids are ranked near the top of the list of most prescribed medications, an attestation to their centrality in the pharmacopoeia [2,3]. Although opioids are the most effective pain relievers available, they are also the most abused class of prescription medications and their rate of abuse continues to rise [4,5]. Physicians thus face a dual imperative of ensuring the availability of opioids to patients with legitimate medical need while minimizing the potential for their misuse.

Concerns over drug misuse in patients treated for chronic pain are legitimate and are not limited to prescribed opioids. Recent studies have reported rates of opioid and/or illicit drug misuse exceeding 25% in both pain management and primary care clinics [6-10]. Thorough and ongoing patient assessment is essential to responsible opioid prescribing, and urine drug testing (UDT) has become a prominent component of this assessment. For example, a 1999 study by Fishman et al [11] revealed that a requirement to submit to random UDT was among the most common features of pain clinic opioid contracts,. A major Veterans Affairs primary care clinic recently implemented a program requiring all potential chronic opioid patients to undergo UDT prior to enrollment [12].

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There is a rationale for this. Evidence indicates that self-reported drug use by chronic pain patients is unreliable [13,14], and behavioral monitoring lacks sufficient sensitivity to detect substance misuse in a substantial percentage of patients. For example, a recent study found that 21% of chronic opioid patients who displayed no aberrant drug-related behaviors had positive UDTs for either an illicit drug or an unauthorized controlled substance [15].

Reviews of opioid prescribing guidelines have advocated the use of UDT in patients who receive chronic opioid therapy. Some of these recommendations discuss the complexities of interpreting the UDT results [16-18], but most do not [5,15,16, 19-23]. These omissions are important in light of reports suggesting that physicians make potentially serious errors in interpreting the results of UDT [24-26].

A few studies have critically assessed the interpretive skills of physicians in regard to UDT. In one study, primary care physicians engaged in the practice of adolescent medicine–nearly all of whom had incorporated UDT in their practice–lacked essential knowledge regarding proper specimen collection and validation, interpretation of positive and negative results, and the need for confirmatory testing [27]. Only 12% of the physicians surveyed knew that oxycodone is not detectable by most opiate screening immunoassays; 40% of physicians knew that poppy seeds could produce a positive screen for opiates; and less than 50% of physicians knew the temporal limits of detection of Δ^9-tetrahydrocannibinol in the urine of regular marijuana users. In a study of emergency department physicians, only 5% correctly identified what substances were detectable by the UDT method used in their hospital, and nearly three quarters of the participants incorrectly believed that all benzodiazepines could be detected [28].

In a survey of UDT interpretive knowledge of physicians in attendance at 3 recent regional opioid education programs, 114 participants completed a 7-item multiple choice questionnaire involving UDT interpretation in patients using prescription opioids, heroin, marijuana, or poppy seed-containing food products. Of 77 physicians who sometimes order UDT, none answered all questions correctly and less than a third answered more than half the questions correctly. Physicians who employed UDT were no more likely to respond correctly to any of the items than physicians who did not employ UDT [29].

This review provides a primer on the most common urine drug testing techniques and discusses the potential pitfalls of interpreting UDT results.

Analytical Methods

The value of a clinical laboratory test can be measured in several dimensions. Economical use of clinical laboratory resources often requires a compromise between the specificity of a particular method and the ability to provide results in a timely and cost-effective manner. This consideration is particularly important in testing for drugs of abuse. Clinical laboratories respond to a variety of demands for relevant information on which patient management is based and UDT services are primarily tailored for the needs of emergency departments [30], where the presence of an illicit drug may influence, for example, the decision whether a patient is a candidate for immediate surgery. In other cases, a positive drug screen may help explain the cause of symptoms that are not consistent with the overall clinical impression. Or the presence of a central nervous system depressant may help guide the management of an unresponsive patient. In such circumstances, the specificity of the drug test is less important than its sensitivity, since a false negative result creates a greater risk of misdirected therapy than a false positive result [31]. Failure to initiate antidotal therapy for a drug overdose ordinarily presents greater risk for the patient than unnecessary administration of an antidote. For these reasons, drug testing methods available in clinical laboratories are designed to be highly sensitive, rapid, and economical.

Screening and confirmatory methods. Analytical methods for detecting drugs in urine fall into 2 categories: screening methods and confirmatory methods. Screening methods are economical and designed to be sensitive, although their specificities vary depending on the particular assay and the likelihood of the presence of similar compounds

that can produce false positive results. Confirmatory methods, on the other hand, are highly specific, but also are expensive and not adaptable to rapid turnaround or high throughput applications. Confirmatory methods ordinarily involve a combination of either liquid or gas chromatographic separation and specific detection by mass spectrometry. When properly designed and performed, confirmatory analytical methods eliminate virtually any chance of a false positive result. Confirmatory methods provide legally defensible drug testing results. Since clinical laboratories are not, typically, held to the same evidentiary standard as forensic toxicology laboratories, routine urine drug testing in clinical laboratories usually involves analytical methods designed for screening purposes.

Sensitivity and Specificity. When a urine drug screen is performed for clinical purposes, with the intention of detecting a specific drug, there are four possible outcomes:

1. True Positive (TP): The result of the test is positive, and the drug is present in the urine.
2. False Positive (FP): The result of the test is positive, but the drug is not present in the urine.
3. True Negative (TN): The result of the test is negative, and the drug is not present in the urine, or is present below the threshold concentration.
4. False Negative (FN): The result of the test is negative, but the drug is present in the urine above the threshold concentration.

These results are summarized in a 2 x 2 table:

	Positive Test	Negative Test
Drug Present	TP	FN
Drug Absent	FP	TN

The sensitivity of a drug screening test, or the test's positivity in the presence of the drug, is calculated in Equation 1:

$$\text{Sensitivity (\%)} = [\ TP / (TP + FN)\ ] \times 100$$

In contrast to sensitivity, the specificity of a drug screening test, or its negativity in the absence of the drug, is calculated by Equation 2:

$$\text{Specificity (\%)} = [\ TN / (TN + FP)\ ] \times 100$$

Predictive value. Sensitivity and specificity are useful measures of the clinical performance of laboratory tests, but they can be misleading because each parameter is calculated presuming the disease (or drug) status of the subject is already known. A sensitivity of 95%, for example, indicates that out of 100 subjects taking a particular drug, 95 will test positive for that drug. But it would be a mistake to assume that, in a subject whose drug status is not known, a positive test provides a 95% certainty of the subject's use of the drug. In clinical practice, a drug screen is typically ordered when the drug status of the patient is unknown, and as a consequence the probability that the test will correctly classify the patient is not predicted by the sensitivity and specificity alone, but it also depends on the pre-test probability that the patient has used the drug.

The predictive value of a drug screen is best illustrated by an example: Suppose that an opiate screen has a sensitivity of 80% and a specificity of 90%, when used to detect the presence of oxycodone in patients who are taking the drug as prescribed. If one-fourth of the patients are not adhering to the prescribed regimen, then random testing of 100 patients will result in 60 true positive results among the adherent group (0.8 x 75), and 2 or 3 false positive results among the non-adherent group (0.1 x 25). The predictive value (PV) of a positive result is the percentage of positive test results that correctly identify adherent patients and it is calculated by Equation 3:

$$PV(+)\ (\%) = [\ TP / (TP + FP)\ ] \times 100$$

Therefore, assuming there were 3 false positive results, the probability that a positive result has identified a patient who is adherent is:

$$PV(+)\ (\%) = [\ 60 / (60 + 3)\ ] \times 100 = 95\%$$

The predictive value of a negative result is:

$$PV(-)\ (\%) = [\ TN / (TN + FN)\ ] \times 100\%$$

In this example, 22 of the 25 non-adherent patients will test negative for the drug, but so will 15 of the adherent patients. The predictive value of a negative result is, therefore:

$$PV(-)\ (\%) = [\ 22 / (22 + 15)\ ] \times 100 = 59\%$$

Only 6 out of 10 negative results will correctly identify non-adherent patients in this scenario.

Predictive value calculations take into account the pre-test probability, which is pivotal in determining the true value of clinical laboratory data. In patients for whom non-adherence is highly likely, the predictive value of a negative result approaches the specificity of the laboratory test, since false negatives will be minimal (see Equation 4). Conversely, in mostly adherent patients, there will be few false positives, and the predictive value of positive results will be high (Equation 3). Hence, the predictive value of a drug screen–or any laboratory test–is contingent upon the clinician's ability to categorize correctly the patient's status prior to the test. Poor clinical judgment compromises the predictive value of laboratory tests, whereas keen clinical skills enhance it. Every laboratory test, including UDT, has limitations in regard to sensitivity and specificity. Clinicians, however, influence the predictive value of laboratory tests by pre-selecting patients who, based on their clinical history, are likely to test positive or negative.

Urine drug screening methods. Most automated urine drug screening methods are based on immunoassay technology, involving a monoclonal antibody that recognizes a structural feature of a drug or its metabolite [32]. The ability of screening techniques to discriminate between the target drug and similar compounds that may be present is determined by the specificity of the antibody. Several immunochemical methods have been adapted to detect therapeutic drugs and drugs of abuse. Most UDT methods involve homogenous immunoassays, the general design of which is illustrated in Fig. 1. In homogeneous immunoassays, binding to the antibody results in a change in some measurable property of the label, and therefore bound labeled antigen can be measured in the presence of unbound labeled antigen. Unlike heterogeneous immunoassays, physical separation of bound and free fractions is not necessary. In some homogeneous immunoassays, the signal generated by the labeled antigens increases in proportion to endogenous (analyte) antigen concentration, while in others the measured signal is inversely proportional to analyte concentration.

The four most common homogeneous immunoassays that have been applied to detecting drugs of abuse in urine are Fluorescence Polarization Immunoassay (FPIA; Fig. 2), Enzyme-Multiplied Immunoassay Technique (EMIT; Fig. 3), Cloned Enzyme Donor Immunoassay (CEDIA; Fig. 4), and Kinetic Interaction of Microparticles in Solution (KIMS; Fig. 5).

Other methods for drug screening. Analytical methods to screen for drugs in urine are not limited to antibody-based assays. Other analytical methods exist, including thin-layer chromatography, high-pressure liquid chromatography, and gas chromatography [33]. These methods offer distinct advantages, primarily with regard to specificity, over immunochemical screening methods, but are not in common use because of the labor and capital investment required to make them routinely available. In addition, turn-around time is a consideration, since hospital laboratories focus primarily on the needs of inpatient and emergency departments. In general, the time required to screen urine specimens for presence of drugs by chromatographic methods is not acceptable to emergency departments, where the primary concern is rapid triage of patients. A thin-layer chromatography drug screening method has been available for many years (Toxi-Lab, MP Products, Amersfoort, Netherlands), but the assay takes 3 to 4 hr. Gas chromatographic methods for drug screening have been described, but they generally require extraction and derivatization steps that are time-consuming [34].

In the 1980s, Bio-Rad Laboratories (Hercules, CA) introduced the REMEDi system, which uses high-pressure liquid chromatography and an array of detectors to screen for drugs of abuse [35]. The system has a reasonably high throughput of about 20 min per specimen, and it screens for a large number of drugs at once. The drug library can be modified by the user, so the instrument can be customized for specific applications.

Chromatographic techniques to screen for drugs are available, including systems that use mass spectrometry to confirm the identity of the drugs that are present, but their use is mostly limited to laboratories that specialize in toxicology, and they are not widely available in hospital-based clinical laboratories.

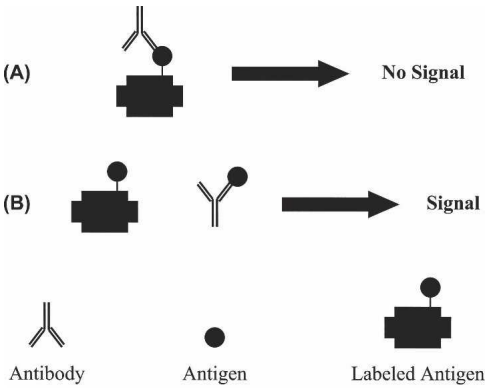

Fig. 1. In a homogeneous, competitive immunoassay, a labeled antigen competes for antibody binding sites with endogenous, unlabeled antigen. In the absence of competing unlabeled antigen, most of the labeled antigen is bound to antibody, changing a measurable property of the label (A). In some cases, antibody binding to antigen results in the suppression of a signal, as in the example illustrated in this figure, but in other designs, a signal is produced when antibody binds to labeled antigen. In the presence of competing unlabeled antigen, labeled antigens are displaced from antibody binding sites, and the signal generated by the label is measurable (B). Homogeneous immunoassays allow measurement of bound or free label without physically separating the two fractions.

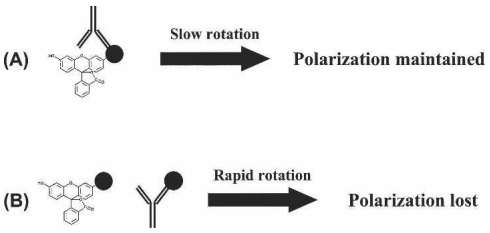

Fig. 2. In the fluorescence polarization immunoassay (FPIA), competing antigen is labeled with fluorescein, which absorbs and fluoresces in a specific plane. In the absence of unlabeled antigen, the fluorescein-labeled antigen is bound to antibody, restricting its movement and resulting in maintenance of the polarization of absorbed light (A). When unlabeled antigen is present, the fluorescein-labeled antigen is displaced from the antibody, and the rotational frequency of the free fluorescein-antigen conjugate is rapid enough to depolarize absorbed radiation (B). In this approach, the signal that is measured, ie, polarization of fluorescence, is inversely proportional to the unlabeled antigen concentration.

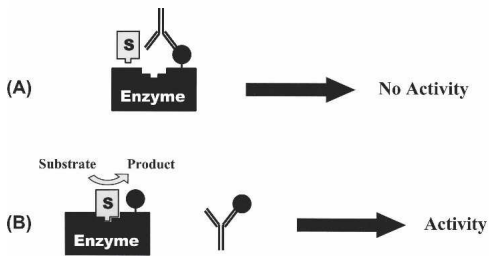

Fig. 3. In the enzyme-multiplied immunoassay technique (EMIT), antigen is bound to an enzyme, glucose-6-phosphate dehydrogenase, so that the presence of an antibody sterically restricts access of the substrate to the active site of the enzyme, and enzyme activity is thereby inhibited (A). Unlabeled, endogenous antigen displaces the enzyme labeled antigens from binding sites on the antibodies, and the unbound enzyme-antigen conjugates provide access for the substrate, allowing conversion to product (B). Enzyme activity is the measured signal, and is proportional to the concentration of unlabeled antigens.

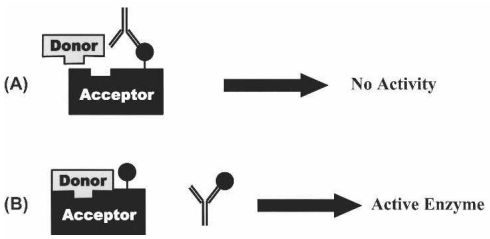

Fig. 4. The cloned enzyme donor immunoassay is based on conjugation of an antigen to a small (donor) fragment of the enzyme β-galactosidase. In solution, donor and acceptor fragments of the enzyme spontaneously combine to form a complete monomer, and four monomers subsequently associate to form the active tetrameric enzyme complex. In the absence of competing unlabeled antigen, antibody binding to the donor-antigen conjugate inhibits combination with the acceptor fragment, and enzyme activity is lost (A). When competing unlabeled antigen is present, the donor-antigen conjugate is displaced from binding sites on the antibody, and is free to combine with acceptor fragments, providing the monomers required for reconstitution of the active tetrameric enzyme. Enzyme activity, therefore, is proportional to the concentration of competing endogenous antigens.

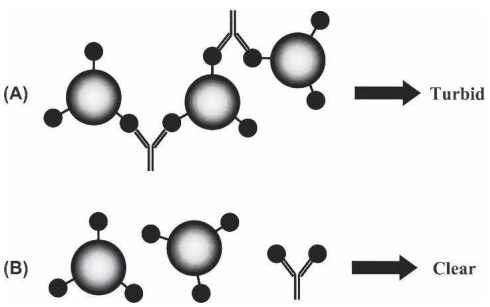

Fig. 5. In the kinetic interaction of microparticles in solution (KIMS) homogeneous immunoassay, antigens are bound to microparticles, which become cross-linked by antibodies, producing large complexes that increase the turbidity of the solution. In the presence of free antigen, however, the antibodies become saturated with unconjugated antigens and are not available to cross-link the antigen-microparticle conjugates. Therefore, turbidity is inversely related to the free, endogenous antigen concentration.

Sensitivity of drug screening immunoassays. In reference to laboratory procedures, "quantitative" customarily refers to methods that yield quantitative results; that is, results that can be expressed as a number along with appropriate units. "Qualitative," on the other hand, describes methods that yield only positive or negative results, providing no information about the concentration or number of measured analyte molecules present. However, even strictly qualitative procedures have a quantitative component, because each is characterized by a threshold concentration, above which the result is reported as positive, and below which the result is reported as negative. Hence, the assay is quantitative to the extent that it provides information about whether the concentration of analyte is above or below a specified quantitative threshold. The distinction between a quantitative and a qualitative result is particularly important with urine drug screens, because "negative" is often interpreted as meaning the drug is not present. But in fact, a negative urine drug screen can be the result of at least 5 different circumstances:

1. There is no drug in the specimen.
2. There is drug in the specimen, but at a concentration below the detection threshold.
3. There is drug in the specimen at a concentration above the threshold, but the assay reacts only weakly with the particular drug that is present.
4. There is interference with the assay, created (unintentionally) by administration of other medications or (intentionally) by addition of adulterants.
5. There is a laboratory error.

Unlike qualitative clinical assays, positive/negative thresholds in UDT are not determined by the inherent detection limit of the method. For most immunochemically-based UDTs, the technology is sufficiently sensitive to detect drug concentrations far below the threshold that is used in the assay [36,37]. Table 1 summarizes the usual threshold concentrations in commercially available urine drug screening methods.

UDT methods are configured to generate negative results below a threshold concentration of drug because the methods are designed to meet the specifications of regulated workplace drug testing programs, which are required to use specific screening threshold concentrations. There are several reasons why workplace drug testing programs require thresholds for drug screening. In some cases, the confirmatory test has a limit of detection higher than that of the screening test, creating the potential for many unconfirmed positive screens if the screening threshold were set too low. For example, immunochemical screening methods for THC react with a broad variety of THC metabolites, whereas the confirmatory method detects only a single metabolite, Δ^9-tetrahydrocannibinol-9-carboxylic acid, which comprises only 15% or so of total metabolites (even though it is the most prominent among the many metabolic products of THC). Therefore, an immunoassay that has a very low detection threshold would yield positive results on specimens in which the Δ^9-tetrahydrocannibinol-9-carboxylic acid concentration is too low to be detected by the confirmatory method [38].

In other cases, cross-reacting compounds that are relatively common (and legal) would cause far too many false positive screening results if the threshold were very low. This is the reason for the relatively high thresholds for amphetamines (1,000 ng/ml), since a variety of non-controlled substances cross-react with the amphetamine immunoassay [39]. Similarly, the opiate threshold of 2,000 ng/ml results from the potential for positive results due to the small amount of morphine and codeine in poppy seeds [40].

Still other thresholds are influenced by legal concerns about the defensibility of positive results.

Table 1. Positive/negative threshold concentrations for several commercially-available urine drug screening methods. Screening thresholds for SAMHSA-sanctioned drug testing are 50 ng/ml for THC and 2,000 ng/ml for opiates. Benzodiazepines and barbiturates are not included in SAMHSA-sanctioned drug testing.

Drug	Positive/Negative Threshold (ng/ml)
THC	50 or 100
Cocaine (as benzoylecgonine)	300
Amphetamines	1,000
Opiates	200, 300, or 2,000
Benzodiazepines	100, 200, or 300
Barbiturates	200

Since marijuana is a drug that is ordinarily smoked, there is a potential for secondhand exposure. As a result, the screening threshold for THC is set high enough to nearly eliminate the possibility of positive results in passively-exposed subjects [41].

An additional consideration in regard to the sensitivity of immunochemical screening methods is that, by design, drug screening immunoassays are only semi-quantitative, based on the signal associated with a particular drug at a specific concentration. Sensitivities may vary to such a degree within a drug class that screening assays may be incapable of detecting specific members of the class. Sensitivity data apply only to a specific drug (or metabolite) and not the entire drug class. Thus, any statement about the analytical sensitivity of an assay must be qualified. For example, a barbiturate assay with a threshold of 200 ng/ml implies that the assay can detect any barbiturate at that concentration, but that is not true. Most barbiturate immunoassays are calibrated with secobarbital, so the 200 ng/ml threshold is only relevant to that particular barbiturate. Phenobarbital, pentobarbital, and amobarbital will be more or less reactive than secobarbital with the reagent antibody, and as a consequence their thresholds of detection vary. When a clinician is attempting to confirm adherence with a prescribed drug regimen, the possibility exists that prescribed doses may produce urinary concentrations that fall below the detection limit when the assay is only weakly reactive with the prescribed drug [30].

Pitfalls in UDT Interpretation

Misinterpretation of positive tests

False positive tests. Cross-reactivities (positive interferences) of immunoassays are due to imperfect assay specificities. Most drugs of concern in clinical drug testing are relatively small molecules with limited antigenic diversity. Therefore, antibodies to these compounds have limited specificity for individual drugs, and some have broad cross-reactivity toward many closely-related compounds [42]. False positive screening assays have been reported for opiates and other drug classes in drug-of-abuse screens–barbiturates, PCP, THC, cocaine, benzodiazepines, and d-amphetamine (Table 2).

Pseudo-false positive tests. This term refers to the (correct) detection of a drug or metabolite in the urine that is not due to administration of the drug itself, but rather to (1) metabolic conversion of an administered drug to another, chemically-related drug, or (2) consumption of a legal substance that contains detectable amounts of a licit or illicit substance.

Several opioids are metabolized to other active opioids. For example, codeine normally undergoes O-demethylation by cytochrome P450 2D6 (CYP 2D6) to produce morphine, although a genetic deficiency in the enzyme necessary for this transformation is not uncommon [43;44]. Thus, in the urine of patients taking codeine, one would ordinarily expect an opiate screening assay to be positive and drug-specific confirmatory tests (GC/MS) to detect both codeine and morphine. Heroin (diacetylmorphine) is metabolically O-deacetylated to 6-monoacetylmorphine and then to morphine, so heroin use will usually produce a positive opiate screen, and confirmatory testing should reveal the presence of morphine and, possibly, 6-monoacetylmorphine. The biological half-life of heroin is very short (just a few min), so the parent drug is usually not detectable. Fig. 6 illustrates the major metabolic pathways for morphine, codeine, and heroin.

Numerous reports have described positive urine screening and confirmatory tests for licit and illicit drugs in patients taking a variety of legal substances–drugs, nutritional supplements, foods, and beverages. An important example is poppy seeds, moderate consumption of which may produce positive screening assays for opiates and positive confirmatory tests for codeine and morphine [45,46]. Another example is coca leaf tea (not produced domestically), which may yield positive screening and confirmatory tests for cocaine [47]. Dronabinol, an FDA-approved cannabinoid for use in chemotherapy-induced nausea and vomiting and for appetite stimulation in AIDS, has a high likelihood of producing positive screening and confirmatory tests for THC [48]. Likewise, studies have documented positive urine screening and confirmatory tests for THC in patients using hemp seed oil, a nutritional supplement purported to be rich in essential fatty acids. Recent reductions in THC content of domestically

Table 2. Selected list of interferences in drug screening tests. Amphet: amphetamines; Benzo: benzodiazepines; Meth: methadone; EMIT, EMIT II (Enzyme-Multiplied Immunoassay Technique), Rapid Test: Dade Behring Incorporated, Deerfield, IL; FPIA (Fluorescence Polarization Immunoassay): Abbott Diagnostics, Abbott Park, IL; CEDIA (Cloned Enzyme Donor Immunoassay): Microgenics, Fremont, CA; OnLine: Roche Diagnostics, Indianapolis, IN; Beckman: Beckman-Coulter Corporation, Fullerton, CA; RapidTech: Genix Technology, Vancouver, BC; DRI: Diagnostic Reagents, Inc., Dearborn, MI; GC-MS: gas chromatography-mass spectrometry.

Drug	Methods	Interferences (positive or negative)	Comments and references
Opiates	EMIT II, FPIA	(-) zolpidem	Dosage tested: 10 mg. [53]
	EMIT	(-) naloxone	Dosage tested: 2 & 4 mg. [54]
	EMIT	(-) dextromethorphan	Dosage tested: 20 & 40 mg. Interference due to structural similarities. [55,56]
	EMIT II	(-) nalmefene	Dosage tested: 2 mg. [57]
	EMIT II	(+) poppy seeds	Positivity directly proportional to amount of poppy seeds ingested. [40,45,46]
	EMIT II, FPIA CEDIA, OnLine Beckman	(+) quinolones: (levofloxacin, ofloxacin, pefloxacin, enoxacin, moxifloxacin, gatifloxacin, trovafloxacin mesylate, sparfloxacin, lomefloxacin, ciprofloxacin, clinafloxacin, norfloxacin, nalidixic acid)	Occurrence of cross-reactivity appears to vary among individual assays. [58] The same drug may produce different results depending on the assay used. [59]
	EMIT	(-) tolmetin	Dosage: 200 & 400 mg. FPIA & GC-MS assays are useful for confirmation. [56,60]
	CEDIA	(+) buprenorphine	To handle cross-reactivity use a different cutoff level for buprenorphine (30 µg/L instead of 5 µg/L). [61]
	Rapid Test Rapid Tech	(+) rifampin	Interference: Syva = 300 mg/L; Genix = 0.05 mg/L. GC-MS yields negative results. [62]
	Unspecified	(+) papaverine	Positive opiate screen following intracavernosal papaverine injection.[63]
THC	EMIT II, FPIA	(-) zolpimen	Dosage tested: 10 mg. [53]
	EMIT	(+) efavirenz	A false positive is unlikely to appear in a confirmatory test. [64,65]
	EMIT, GC-MS	(+) hemp seed	No specimens gave a GC-MS quantitative value above the limit of detection for marijuana. [66,67]
	EMIT	(-) ibuprofen, naproxyn, fenoprofen	Believed to cause interference with the methylation of THC-COOH. [68,69] Unlikely to cause a positive result. Should verify result with GC/MS.
	EMIT	(-) tolmetin	Dosage: 200 & 400 mg. Interferes with THC detection due to its similar molar absorptivity. TDx and GC-MS will detect THC. [60]
	EMIT	(+) pantoprazole	Verify results by a confirmatory test. [70]
Cocaine	EMIT II, FPIA	(-) zolpimen	Dosage tested: 10 mg. [53]
	FPIA, GC/MS	(+) coca leaf tea	Dosage: 1 cup of tea. Significant amounts of cocaine & related alkaloids are present. [47]
	EMIT, EMIT II	(-) salicylates	Negative bias seems related to the reagent system, not directly to the analyte. Probably due to enzyme inhibition [71,72]
	GC-MS	(-) fluconazole	Does not interfere with the EMIT screening assay, Transformation of benzoylecgonine (major cocaine metabolite) can eliminate this interference. [73,74]

(continued on facing page)

Table 2 (continued).

Drug	Methods	Interferences (positive or negative)	Comments and references
Amphet	EMIT II. FPIA	(-) zolpimen	Dosage tested: 10 mg. [53]
	EMIT	(+) phenylpropanolamine fenfluramine ephedrine	GC-MS can make the differentiation.[75]
	EMIT	(-) tolmetin	Dosage: 200 & 400 mg. Interferes with amphetamine detection due to similar molar absorptivity. GC-MS will detect the presence of amphetamine. [60]
	FPIA, GC-MS	(+) selegiline	[76]
	EMIT	(+) phentermine	Structural similarities give cross-reactivity. GC-MS is unaffected. [77]
	EMIT	(+) trazodone	Cross-reactivity due to drug metabolites rather than parent compound. Results should be verified with GC-MS. [78]
	EMIT	(+) bupropion	Parent drug added to urine did not give a positive screen. Cross-reactivity may be due to a bupropion metabolite. [79]
Benzo	EMIT, FPIA	(-) zolpimen	Dosage tested: 10 mg. [53]
	EMIT, FPIA CEDIA	(+) oxaprozin	Dosage tested: 1200 mg. A confirmatory test is recommended. [80]
	FPIA	(+) fenoprofen, flurbiprofen, indomethacin, ketoprofen, tolmetin	High drug concentrations are needed. [60]
Meth	DRI	(+) verapamil	Screening threshold = 300 ng/ml. [81]

manufactured hemp seed oil, however, make it an unlikely cause of positive UDT when used at recommended doses and when tested at the federally-mandated cutoff of 50 ng/ml [48].

Laboratory error. Because clinical drug testing is not subject to the Mandatory Guidelines for Federal Workplace Drug Testing Programs, including observed collections, strict chain of custody procedures, specimen integrity assessment, and split specimens, it is subject to the same potential for technical and clerical errors as all laboratory tests, eg, specimen mix-ups, mislabeling, reporting errors, etc. Although the occurrence of these types of errors is rare, and investigation by the laboratory often finds that the error is correctable, analysis of a repeat specimen may be indicated in circumstances when the reliability of a test result is in doubt.

Misinterpretation of negative tests

False negative tests. There are many potential reasons for false negative tests: intentional urine tampering for the purpose of defeating urine drug screening or confirmatory testing; unintentional co-administration of negative interferants; use of an assay not designed to detect the drug of interest; and assay cut-off above the urinary concentration of the drug or metabolite.

Urine tampering comprises a variety of in vivo and in vitro techniques. In vivo methods include ingestion of sodium bicarbonate, diuretics, salicylates, and commercial body "cleansers" (eg. XXTra Clean; Green Clean) to alter the chemical composition or concentration (specific gravity) of urine. In vitro methods include specimen dilution, specimen substitution with drug-free human, animal, or synthetic (eg, Dr. John's Concentrated Urine; Sub-Solution) urine, and specimen adulteration with assay interferants (eg, UrineLuck, Instant Clean Add-it-ive). In workplace drug testing programs, specimen integrity is checked at the collection site and assessed in the laboratory. Specimens for forensic drug tests should have the characteristics of freshly voided human urine, such as: (1) temperature 90° to 100° F within 4 min of voiding, (2) pH 4 to 9, (3) creatinine level ≥20 mg/dl, and (4) a specific gravity of 1.003 to 1.030.

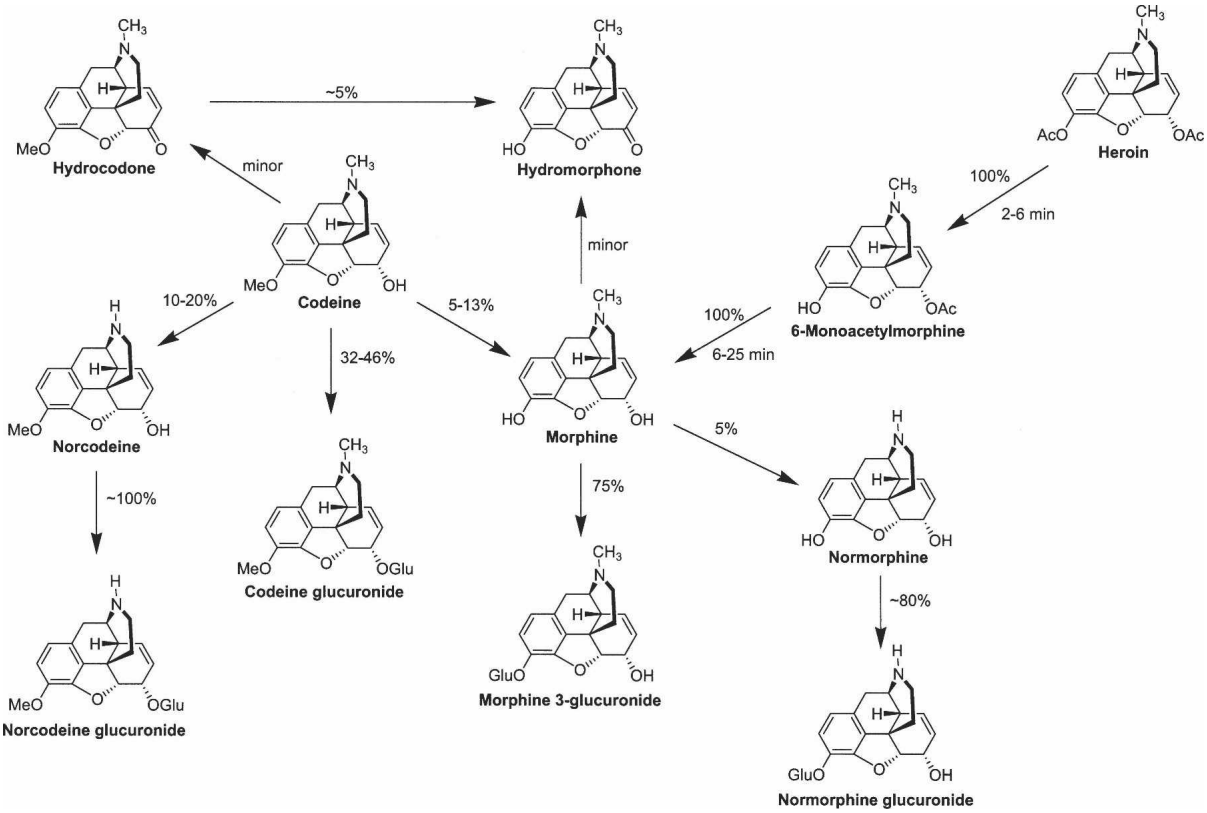

Fig. 6. Metabolic pathways for morphine, codeine, and heroin. Percentages indicate the approximate amount of compound converted the indicated metabolite, based on 24-hr urinary recoveries of the various compounds [82]. Morphine-6-glucuronide and morphine-3,6-diglucuronide are minor metabolites. For heroin and its metabolite, 6-monoacetylmorphine, the half-lives for the two successive O-deacetylations are indicated. O-Demethylation of codeine and hydrocodone to produce morphine and hydromorphone, respectively, requires a specific CYP450 enzyme that is deficient in approximately 7% of Caucasians and about 50% of Chinese [43,44]. Small amounts of hydromorphone have been detected in the urine of patients treated with morphine, suggesting a minor metabolic pathway involving oxidation at the C-6 position [83]. Metabolic conversion of codeine to hydrocodone has also been demonstrated [84].

Some adulterants are designed to interfere with the assay itself, and are not detectable by routine integrity checks for substitution or dilution. Such agents include nitrites, chromates, halogens, glutaraldehyde, pyridine, and surfactants. Most of these adulterants can be detected in the laboratory by individual or multiple tests designed specifically to detect specimen adulteration. In an increasingly sophisticated game of cat and mouse, as the proprietary ingredients in commercially available urine adulterants become known and as tests are developed to detect them, manufacturers of these adulterants reformulate their products in order to avoid detection. False negative urine screens may also result from co-administration of a number of prescription and over-the-counter drugs (Table 2).

Assay is not designed to detect drug. Opiate screens are generally designed to detect opiates–codeine and morphine–along with a variety of congeneric drugs and metabolites. Although these assays have varying degrees of cross-reactivity, unless designed to detect specific opioids (eg, methadone, fentanyl, oxycodone, propoxyphene), many class-specific screening tests will fail to detect these drugs when administered in therapeutic doses (Table 3). Moreover, screening assays intended to detect illicit use are not always capable of detecting therapeutic concentrations of slightly reactive drugs within a particular class. For example, a 2000 ng/ml cut-off for opiates may fail to detect a drug in patients who (1) have not used the drug in 1 to 3 days, (2) display accelerated metabolism of the drug, or (3) are

.Table 3: Percent cross-reactivity of several commercially-available urine opiate screening methods with opiate metabolites and analogues. With the exception of the DRI oxycodone method, all of the methods are calibrated with morphine. Zeros indicate no measurable cross-reactivities, and blank entries indicate that the particular compound was not tested. Entries preceded by a "greater than" (>) or "less than" (<) sign indicate the reciprocal percent of calibrator concentration required to produce a negative or positive screening result, respectively. (eg, in an assay calibrated to produce a positive result at a morphine concentration of 300 ng/ml, ">50" indicates that 600 ng/ml of the analogue produced a negative result; "<25" indicates that 1,200 ng/ml of the analogue produced a positive result) [1]Roche Diagnostics, Indianapolis, IN; [2]Dade-Behring, Deerfield, IL; [3]Abbott Diagnostics, Abbott Park, IL; [4]Microgenics, Fremont, CA.

	Online DAT opiates II[1] assay	EMIT II+ opiate aassay[2]	TDx/TDx-flex opiate opiate assay[3]	Archetict/ Aeroset	AsSym opiate[3]	CEDIA opiate[4]	DRI opiate[4]	DRI oxycodone[4]
Morphine	100	100	100	100	100	100	100	<29
Codeine	134	98	>3.6	167	>3.6	125	167	<20
Ethyl morphine	101		<10		>100			
Diacetyl morphine (heroin)	82					53	86	<33
6-Acetylmorphine	78	69	>20	67	<30	81	79	<200
Dihydrocodeine	69	103	>3.6	106	>3.6	50	67	<100
Morphine-3-glucuronide	54	48	>57	47	>57	81	50	<11
Morphine-6-glucuronide			>5.7		<8.6	47	100	
Hydrocodone	28	121	>8.0	158	>12	48	18	<133
Hydromorphone	21	60	>4.4	54	>6.7	57	7.5	<333
Norcodeine	2							<10
Normorphine							0	<10
Oxycodone	0	12	>1.1	11	<1.7	3.1	1.9	100
Oxymorphone		1.5	<10	0	<15	1.9	0.7	103
Noroxycodone								<0.1
Noroxymorphone								<0.1
Meperidine	0	<0.6	<2.0	0	<3.0	0.2	0	
Levallorphan		<4	<6.0	13	<6.0			
Levorphanol		29	>6.0	27	>6.0		2.1	<50
Nalorphine		3	<20	2.3	<30			
Naloxone	0	0.04	<20	0	<30		0	<50
Imiprimine	0					1.6		
Ranitidine						0	0	
Thebaine	25		<20		<30		<15	
Naltrexone	0						0	<20
Fentanyl			<40		<60			

taking an opioid that is only slightly reactive with the opiate screening assay.

Pseudo-false negative tests. This term refers to screening and confirmatory tests that (correctly) fail to demonstrate a drug in the urine of patients who are using the drug as prescribed. These negative tests are most likely to occur in patients who, for environmental or genetic reasons, display accelerated metabolism of the drug of interest. For example, a recent case report [49] described a patient who claimed to be using controlled-release oxycodone (20 mg, po, every 12 hr) and immediate-release oxycodone (5 mg, po, every 6 hr as needed). The patient repeatedly tested negative for oxycodone by GC/MS, a confirmatory method. Subsequent analysis for oxycodone metabolites supported the patient's claim of adherence to the prescribed opioid regimen. In this case, co-administered rifampin, a CYP 3A4 and 2D6 inducer, appeared to be responsible for the accelerated metabolism of the opioid and, hence, this pseudo-false negative test. Some populations are genetically ultra-rapid metabolizers, owing to gene duplication or multi-duplication. For example, approximately 30% of Ethiopians [50] and 20% of Saudi Arabians [51] are genetically CYP 2D6 ultra-rapid metabolizers.

Post-analytical errors. Von Seggern et al [24] described a case of a negative urine opiate screen in

a patient who was prescribed controlled-release oxycodone (20 mg, po, every 6 hr). On inquiry, the testing laboratory stated–incorrectly–that its immunoassay would detect oxycodone. On the basis of this information the patient was dismissed from the authors' practice. (A family member subsequently consulted independent toxicologists who confirmed the possibility of a false negative opiate immunoassay for oxycodone. Re-testing of the original urine sample using GC/MS demonstrated oxycodone at a level consistent with prescription adherence.) This report highlights the fact that most laboratory-associated errors occur not in the analytical phase, but in the pre- and post-analytical phases [52]. Close communication with the laboratory's director or toxicologist can minimize the potential for such errors.

Conclusions

Urine drug testing can be a valuable component in the care of the patient on chronic opioid therapy, but interpretation is highly complex and dependent on a host of patient and laboratory variables. Available data suggest serious deficiencies in physicians' abilities to accurately interpret urine drug test results, and the consequences of misinterpretation are potentially serious. Misinterpretation of negative UDT results may lead the clinician to a false sense of assurance that substance misuse does not exist. Misinterpretation of positive UDTs may have negative consequences for the patient stemming from false accusations of misuse, including: (1) unjustified loss of opioid privileges, (2) loss of physician-patient relationship, (3) painful and possibly dangerous opioid withdrawal, (4) compromised ability to receive appropriate therapy from future physicians (as responsible physicians will request medical records from previous providers before prescribing controlled substances), and (5) involvement of law enforcement [29]. Clinical urine drug testing should therefore be embarked upon only with a sound basic knowledge of the capabilities and limitations of each specific test. Unexpected results should be subjected to appropriate confirmatory testing. Consultative support from a laboratory director, toxicologist, or certified medical review officer is essential. Finally, urine drug testing should be only one component of a comprehensive, compassionate, and ethical plan of patient care.

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