

Urine Drug Screening: Practical Guide for Clinicians

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Drug testing, commonly used in health care, workplace, and criminal settings, has become widespread during the past decade. Urine drug screens have been the most common method for analysis because of ease of sampling. The simplicity of use and access to rapid results have increased demand for and use of immunoassays; however, these assays are not perfect. False-positive results of immunoassays can lead to serious medical or social consequences if results are not confirmed by secondary analysis, such as gas chromatography–mass spectrometry. The Department of Health and Human Services' guidelines for the workplace require testing for the following 5 substances: amphetamines, cannabinoids, cocaine, opiates, and phencyclidine. This article discusses potential false-positive results and false-negative results that occur with immunoassays of these substances and with alcohol, benzodiazepines, and tricyclic antidepressants. Other pitfalls, such as adulteration, substitution, and dilution of urine samples, are discussed. Pragmatic concepts summarized in this article should minimize the potential risks of misinterpreting urine drug screens.

Mayo Clin Proc. 2008;83(1)66-76

6-MAM = monoacetylmorphine; BAC = blood alcohol concentration; DHHS = Department of Health and Human Services; EMIT = enzyme-multiplied immunoassay technique; FPIA = fluorescence polarization immunoassay; GC-MS = gas chromatography–mass spectrometry; MDMA = methylenedioxy-methylamphetamine; NSAID = nonsteroidal anti-inflammatory drug; PCC = pyridinium chlorochromate; PCP = phencyclidine; RIA = radioimmunoassay; TCA = tricyclic antidepressant; THC = tetrahydrocannabinol; UAC = urine alcohol concentration; UDS = urine drug screen

Drug testing beyond the health care and criminal justice systems has increased throughout the past decade. Common areas for drug testing include the workplace (eg, preemployment and random testing), the military, athletics, legal and criminal situations (eg, postaccident testing, rehabilitation testing of ex-convicts), and health care (eg, treatment, compliance monitoring, cause of death). Misinterpretation of drug tests can have serious consequences, such as unjust termination from a job, risk of prison sentence, inappropriate exclusion from a sporting event, and possibly inappropriate medical treatment in emergencies.

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Our goal is to provide clinically relevant information that can be used to interpret urine drug screens (UDSs) for commonly abused drugs (ie, alcohol, amphetamines, benzodiazepines, opioids, marijuana, cocaine, phencyclidine [PCP], and tricyclic antidepressants [TCAs]). Proper evaluation of urine specimens, including detection times, are discussed, as well as false-positive results and potential false-negative results. Interpretation of tests for performance-enhancing drugs is beyond the scope of this article and is not discussed.

METHODS OF DRUG TESTING

Urine, blood, hair, saliva, sweat, and nails (toenails and fingernails) are some biological specimens used to perform laboratory drug testing, and they provide different levels of specificity, sensitivity, and accuracy. Urine is most often the preferred test substance because of ease of collection. Concentrations of drugs and metabolites also tend to be high in the urine, allowing longer detection times than concentrations in the serum allow.¹

Two types of UDSs are typically used, immunoassay and gas chromatography–mass spectrometry (GC-MS). Immunoassays, which use antibodies to detect the presence of specific drugs or metabolites, are the most common method for the initial screening process. Advantages of immunoassays include large-scale screening through automation and rapid detection.² Forms of immunoassay techniques include cloned enzyme donor immunoassay; enzyme-multiplied immunoassay technique (EMIT), a form of enzyme immunoassay; fluorescence polarization immunoassay (FPIA); immunoturbidimetric assay; and radioimmunoassay (RIA). In addition, immunoassay techniques are used in many home-testing kits or point-of-care screenings.

The main disadvantage of immunoassays is obtaining false-positive results when detection of a drug in the same class requires a second test for confirmation. Results of immunoassays are always considered presumptive until confirmed by a laboratory-based test for the specific drug (eg, GC-MS or high-performance liquid chromatography). Yet even GC-MS can fail to identify a positive specimen (eg, hydromorphone, fentanyl) if the column is designed to detect only certain substances (eg, morphine, codeine).³

Gas chromatography–mass spectrometry is considered the criterion standard for confirmatory testing. The method is able to detect small quantities of a substance and confirm the presence of a specific drug (eg, morphine in an opiate screen). It is the most accurate, sensitive, and reliable method of testing; however, the test is time-consuming, requires a high level of expertise to perform, and is costly. For these reasons, GC-MS is usually performed only after a positive result is obtained from immunoassay.

In postmortem analyses, lactate dehydrogenase and lactate were found to interfere with assays for commonly abused substances (amphetamine, barbiturates, benzodiazepines, opiates, and propoxyphene).⁴ Additional confirmatory testing is advised for patients who have illnesses that increase the risk of lactic acidosis, such as diabetes mellitus, liver disease, and toxin ingestion (eg, ethanol, methanol, salicylates).

CUTOFF LIMITS

The Department of Health and Human Services (DHHS) has established specific cutoff levels that define a positive result for the workplace (Table 1⁵). These values were developed to help eliminate false-positive results (eg, poppy seeds causing positive opium results). Values below the cutoff levels are reported as negative, which can lead to false-negative results. These values from the DHHS were established for the workplace only, and the role of these threshold levels in clinical settings (eg, health care, substance abuse programs) remains controversial because of the potential for false-negative results. Cutoff levels were developed for adults, and values might need to be lowered for children because their urine is more dilute than that of adults.⁶ All laboratories should evaluate cutoff values for their specific patient populations.

DETECTION TIMES

Several factors need to be considered to determine the length of time a drug or substance can be detected in the urine. Pharmacokinetics, presence of metabolites, patient variability (eg, body mass), short-term vs long-term use of a drug, pH of the urine, and time of last ingestion are some factors that influence detection times. Table 2⁷⁻¹² reports usual detection times for drugs of abuse discussed in this article.

EVALUATION OF URINE SAMPLES

Adulterating, substituting, and diluting urine samples are common practices used to avoid detection of drug use. Understanding specific characteristics of a urine specimen can help in identifying false-negative results.

TABLE 1. Federal Workplace Cutoff Values^a

Substance	Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GC-MS) (ng/mL)
Marijuana metabolites ^b	50	15
Cocaine metabolites ^c	300	150
Opiate metabolites	2000	2000
Phencyclidine	25	25
Amphetamines	1000	500
Methamphetamine ^d	Incomplete data	500

^a GC-MS = gas chromatography–mass spectrometry.

^b Delta-9-tetrahydrocannabinol-9-carboxylic acid.

^c Benzoylcegonine.

^d Specimen must also contain amphetamine at a concentration greater than or equal to 200 ng/mL.

Data from reference 5.

The first step in evaluating a urine sample is documentation of the appearance and color. Urine specimens should be shaken to determine whether such substances as soap have been added to the urine. Excessive bubble formation that is long lasting can indicate an attempt to adulterate the specimen.¹³ Liquid drain cleaner, chlorine bleach, liquid soap, ammonia, hydrogen peroxide, lemon juice, and eyedrops have been used to manipulate the urine. Other commercial products containing glutaraldehyde, sodium or potassium nitrate, peroxide and peroxidase, and pyridinium chlorochromate (PCC) are being sold to falsify urine specimens.¹⁴ Tetrahydrocannabinol (THC) assays tend to be the

TABLE 2. Length of Time Drugs of Abuse Can Be Detected in Urine

Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Data from references 7 through 12.

most sensitive for adulterants causing false-negative results.¹⁵ Normally, urine specimens range from pale yellow to clear depending on concentration.¹⁶ Urine specimens collected in the early morning are the most concentrated and often provide the most reliable information.¹⁰ Unusual colors in urine samples can be due to medications, foods, or diseases and should be noted on documentation that accompanies the specimen for evaluation.¹⁷

The urine specimen temperature should be recorded within 4 minutes of collection; the temperature should be 32 C to 38 C initially and can remain warmer than 33 C for up to 15 minutes.¹⁶ Temperatures outside this range can indicate that a substituted urine sample was used. The pH for normal urine fluctuates throughout the day but usually is in the range of 4.5 to 8.0. Specimen contamination should be suspected if the pH level is less than 3 or greater than 11 or if the specific gravity is less than 1.002 or greater than 1.020.¹⁶ Creatinine concentrations in normal human urine should be greater than 20 mg/dL. Urinary creatinine concentrations of less than 20 mg/dL are considered dilute, whereas concentrations of less than 5 mg/dL are inconsistent with human urine.¹⁰ Urinary nitrite levels should be less than 500 µg/mL.¹⁶ If adulteration is suspected or results fall outside these ranges, another specimen should be collected under direct, observed supervision.

Devices such as the Intect 7 (Branan Medical Corp, Irvine, CA), Mask Ultra Screen (Kacey, Asheville, NC), AdultaCheck 4, and AdultaCheck 6 (both from Chimera Research and Chemical Inc, Tampa, FL) have been developed to assess the integrity of urine samples.¹⁴ These tests all detect validity parameters, such as creatinine and pH, but vary in their detection of adulterants, such as bleach, glutaraldehyde, PCC, nitrites, and oxidants. Two recent studies have shown the Intect 7 to be the most sensitive for adulterations because it can detect bleach, PCC, and vinegar.^{18,19} These devices are often used in conjunction with urine drug testing.

SPECIFIC DRUGS TESTED IN THE URINE

The DHHS guidelines for workplace urine testing include 5 mandated drugs of abuse (amphetamines, cannabinoids, cocaine, opiates, and PCP); however, several other substances can be abused (eg, benzodiazepines), warranting screening for more than the 5 mandated drugs of abuse. Urine drug screens for alcohol, benzodiazepines, methadone, and TCAs could be of interest to clinicians in various settings and are also discussed in this article. Table 3^{1,8,16,20-81} summarizes false-positive results sometimes seen with these abused substances. Overall risk of having a false-positive result due to cross-reactivity on immunoassays depends largely on the specific test (eg, EMIT, FPIA, RIA) used and

the specific substance for which the person is being tested. Several studies have evaluated the risk of false-positive results and have found high positive predictive values for cocaine (92.1; 97.8)^{82,83} and THC (92.2; 100)^{82,83} in contrast to low positive predictive values for opiates (71.2)⁸² and amphetamines (74.1).⁸³

ALCOHOL

Alcohol, a substance legal for adults in the United States to ingest, is the most widely used substance of intoxication in the world.⁷ It is rapidly metabolized in the human body. Approximately 90% to 95% is oxidized in the liver by alcohol and aldehyde dehydrogenase and the microsomal ethanol-oxidizing system before elimination in the urine.⁸⁴ Only 1% to 2% of ingested alcohol is excreted unchanged in the urine.⁸⁵ Urine alcohol concentration (UAC) follows a variable pattern when compared with blood alcohol concentrations (BACs). During alcohol ingestion (ie, the early absorptive phase), the UAC is less than the BAC. A 1.0 to 1.2 ratio of UAC to BAC is noted during the late absorptive phase (ie, >60 minutes after intake). The UAC in the postabsorptive phase is always greater than the BAC. Thus, the UAC result from the postabsorptive phase should be divided by 1.3 to extrapolate a BAC value from the urine sample.⁸⁵ This calculated value is useful in estimating the BAC at the time of specimen collection but cannot be used to estimate impairment after alcohol ingestion. Factors to be considered when evaluating the results of a UAC include the quantity of alcohol ingested, time between collection and last alcohol intake, and concentration of urine. In addition to urine screens, several other physiologic biomarkers (ie, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, carbohydrate-deficient transferrin, ethyl glucuronide) are used to assess alcohol intake, but these tests entail laboratory analysis of blood.⁸⁶ In clinical settings, urine alcohol screens are used far less frequently than breath or blood tests.¹⁵

AMPHETAMINES

Amphetamines are among the 5 drug assays required by the DHHS. Amphetamines and methamphetamines are available by prescription for therapeutic use; however, amphetamines are commonly abused for their stimulant and euphoric effects. Most amphetamine assays are designed to detect amphetamine, racemic compounds (eg, dextroamphetamine, methamphetamine), and illicit analogues (methylenedioxyethylamphetamine, methylenedioxyamphetamine, and methylenedioxymethylamphetamine [MDMA]). Unfortunately, other stimulants, anorexiant, and chemically related compounds (eg, pseudoephedrine), have been shown to produce false-positive results, making

TABLE 3. Summary of Agents Contributing to Positive Results by Immunoassay^a

Substance tested via immunoassay	Potential agents causing false-positive result	Substance tested via immunoassay	Potential agents causing false-positive result			
Alcohol ²⁰	Short-chain alcohols (eg, isopropyl alcohol)	Cannabinoids ^{1,8,43-48}	Dronabinol Efavirenz			
Amphetamines ²¹⁻⁴⁰	Amantadine	Cocaine ⁴⁹⁻⁵¹	Hemp-containing foods NSAIDs Proton pump inhibitors Tolmetin			
	Benzphetamine		Opioids, opiates, and heroin ^{8,16,52-63}	Coca leaf tea Topical anesthetics containing cocaine		
	Bupropion			Phencyclidine ^{8,52,64-70}	Dextromethorphan Diphenhydramine ^e Heroin	
	Chlorpromazine				Tricyclic antidepressants ⁷¹⁻⁸¹	Opiates (codeine, hydromorphone, hydrocodone, morphine)
	Clobenzorex ^b					Poppy seeds
	<i>l</i> -Deprenyl ^c					Quinine
	Desipramine					Quinolones
	Dextroamphetamine					Rifampin
	Ephedrine					Verapamil and metabolites ^c
	Fenproporex ^b					Dextromethorphan Diphenhydramine ^e
	Isometheptene	Doxylamine				
	Isoxsuprine	Ibuprofen				
	Labetalol	Imipramine				
	MDMA	Ketamine				
	Methamphetamine	Meperidine				
	<i>l</i> -Methamphetamine (Vick's inhaler) ^d	Mesoridazine				
	Methylphenidate	Thioridazine				
	Phentermine	Tramadol				
	Phenylephrine	Venlafaxine, O-desmethylvenlafaxine				
	Phenylpropanolamine	Carbamazepine ^f				
	Promethazine	Cyclobenzaprine				
Pseudoephedrine	Cyproheptadine ^f					
Ranitidine	Diphenhydramine ^f					
Ritodrine	Hydroxyzine ^f					
Selegiline	Quetiapine					
Thioridazine						
Trazodone						
Trimethobenzamide						
Trimipramine						
Oxaprozin						
Sertraline						

^aMDMA = methylenedioxyamphetamine, NSAID = nonsteroidal anti-inflammatory drug.

^bApproved in Mexico. Not approved in the United States.

^cConverts to *l*-methamphetamine and *l*-amphetamine.

^dNewer immunoassays have corrected the false-positive result for Vick's inhaler.

^eDiphenhydramine and verapamil (including metabolites) have been shown to cause positive results in methadone assays only.

^fReports of false-positive results occurred with serum only.

the amphetamine assay one of the most difficult tests to interpret. The Figure illustrates common medications with structures similar to amphetamines that can produce false-positive results.

Interpretation of amphetamine assays requires a detailed medication history that includes over-the-counter, prescription, and herbal medications. Pseudoephedrine, ephedrine, phenylephrine, and decongestants common in over-the-counter cold medicines are known to cross-react with the amphetamine assay.³⁹ Results of amphetamine assays are often positive among patients taking prescription stimulants for attention deficit and hyperactivity disorder, for narcolepsy, and as anorexiant because many of these stimulants contain amphetamines (Table 3). Many psychotropic medications, such as bupropion,^{33,40} phenothiazines (eg, chlorpromazine, promethazine, and thioridazine),^{29,34} trazodone,³⁷ and TCAs (desipramine and doxepin),^{30,31} have

been reported to interfere with immunoassays. Most of these reports attribute the cross-reactivity to metabolites of these agents, which typically are not assessed in manufacturers' evaluations of immunoassays for interference. Other unique agents found to cross-react with the amphetamine immunoassay include labetalol,²³ isometheptene,²⁷ ranitidine,^{24,26,35} ritodrine,³² and trimethobenzamide.^{22,25} Structural similarities are the main reasons for the interference.

Another confounding factor for the amphetamine immunoassay is the inability to distinguish between the 2 isomers of methamphetamine, *d*-methamphetamine and *l*-methamphetamine (*l*-desoxyephedrine). The *d*-isomer is responsible for the central nervous system stimulant effects, whereas the *l*-isomer mainly works peripherally and does not possess euphoric effects.¹⁵ Vicks nasal inhaler contains *l*-methamphetamine and did cross-react with older

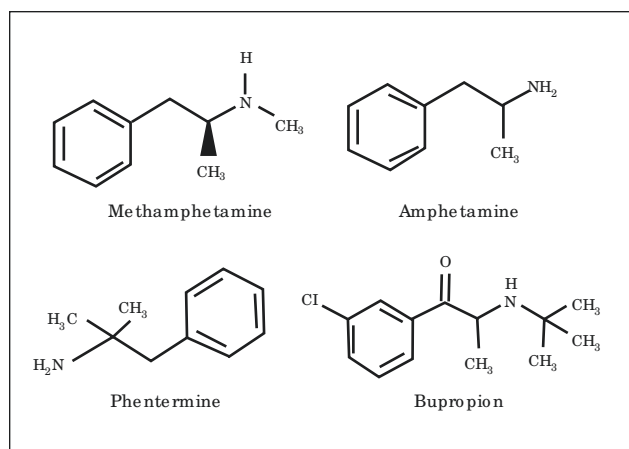


FIGURE. Agents that can cause positive results on amphetamine immunoassay. Adapted from ChemIDplus Lite. US National Library of Medicine, National Institutes of Health. Available from: <http://sis.nlm.nih.gov/chemical.html>. Accessed December 7, 2007.

immunoassay tests when used in large quantities. Newer EMIT tests have shown no positive results with the Vicks nasal inhaler when used up to twice the recommended dose.³⁶ Additionally, selegiline and deprenyl, agents used for the treatment of Parkinson disease and depression, produce *l*-amphetamine and *l*-methamphetamine metabolites, which give a positive result on immunoassays.³⁸ Unfortunately, routine GC-MS also does not distinguish between the 2 isomers and requires chiral chromatography to differentiate between the *d*- and *l*- forms.²¹

An added problem of amphetamine immunoassays is their low sensitivity for detection of MDMA.⁸⁷ Common monoclonal amphetamine and methamphetamine immunoassays (eg, EMIT, FPIA, and RIA) can detect MDMA because of cross-reactivity; however, sensitivity for MDMA is approximately 50% less than for amphetamine and methamphetamine.^{88,89} High concentrations of MDMA in the urine are needed to elicit positive results on amphetamine immunoassays. However, specific tests have been designed to incorporate 3 monoclonal antibodies specific for amphetamine, methamphetamine, and MDMA, resulting in greater sensitivity for detection of MDMA.⁸⁷ These tests should be considered if MDMA use is suspected.

BENZODIAZEPINES

Benzodiazepines belong to a class of prescribed drugs that are widely used for a variety of medical and psychiatric conditions. Benzodiazepines bind to the benzodiazepine site at the γ -aminobutyric acid type A receptor, which is the main inhibitory neurotransmitter in the central nervous system. Benzodiazepines, which are structurally similar with differences primarily in pharmacokinetic parameters (eg, onset of effect, half-life, metabolites), have 4 pharma-

cologic properties: (1) sedative-hypnotic, (2) anxiolytic, (3) antiepileptic, and (4) muscle relaxant activities.⁹⁰ Benzodiazepines cause sedation, impaired memory, cognitive impairment, and disinhibition. They have also been associated with paradoxical effects (such as increased agitation and insomnia), especially in pediatric and elderly patients.⁹¹ Although all benzodiazepines can be abused, agents that have the shortest half-life with the highest potency (eg, alprazolam, triazolam) and greatest lipophilia (eg, diazepam) tend to have the most abuse potential.⁹² Benzodiazepines are often abused for their euphoric effects (along with other abused substances, such as alcohol).

The widespread use of benzodiazepines makes it difficult to distinguish between pharmacologic use vs abuse of these substances with a UDS. In addition, detection of benzodiazepines on assays will not establish single use vs long-standing use, abuse, or dependence. Anxiolytic agents, such as lorazepam, are often used in emergency departments for sedation and control of acute agitation; therefore, a thorough medication history is warranted to prevent misinterpretation of a positive benzodiazepine result. Detection of benzodiazepines in the urine by commercially available assays is primarily based on detection of oxazepam and nordiazepam, the primary metabolites of many of the benzodiazepine drugs.^{93,94} Yet assays are unable to distinguish between individual benzodiazepines. The standard cutoff levels of benzodiazepines are set by DHHS and are listed in Table 1.⁵ After ingestion, highly lipophilic agents (eg, diazepam) are detected within minutes in serum and within 36 hours in the urine.⁹⁵ Agents that are extensively metabolized with long half-lives (eg, diazepam, chlordiazepoxide) can be detected in the urine up to 30 days after ingestion. As noted previously, extensively metabolized drugs are detected in the urine as their metabolites, not as the parent drug.

Recently, several published reports described the use of hair and urine samples for detection of benzodiazepine drugs in forensic cases (eg, drug-facilitated sexual assault)⁹⁶⁻⁹⁸; therefore, clinicians need to become more familiar with interpreting results from screening tests.

Few reports assess agents that produce false-positive or false-negative results on benzodiazepine screens. Sertraline and oxaprozin have been identified as agents that have cross-reactivity with benzodiazepines. Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID) marketed for treatment of rheumatic arthritis and osteoarthritis.⁴² Plasma concentrations of the drug are found within 3 to 6 hours after ingestion.⁴¹ In one report, 2 patients tested positive for diazepam after taking oxaprozin. Both patients had a negative urine panel after discontinuing oxaprozin (4-7 days after cessation of the drug).⁴² In follow-up documentation, 1200 mg of oxaprozin for 1 day produced a

positive result on the benzodiazepine panel, although 600 mg of ibuprofen twice daily and 500 mg of naproxen twice daily did not produce positive results. Oxaprozin is not structurally related to benzodiazepines,⁴¹ and whether other NSAIDs can also produce similar positive results is unknown.⁹⁹ Recently, the prescribing information for oxaprozin was revised to state that false-positive tests for benzodiazepines have been reported in patients who take the NSAID. The effect can last up to 10 days after drug discontinuation, and confirmatory testing by GC-MS is recommended. Some evidence suggests that compounds with various differences in chemical structure, such as midazolam, chlordiazepoxide, and flunitrazepam, are not detected in many assays. Detection tends to be manufacturer- and antibody-specific.^{100,101}

CANNABINOIDS

Cannabis (hemp plant), also referred to as *marijuana*, was the most commonly used illicit drug in 2005.¹⁰² *Cannabinoids* refers to a unique subset of chemicals found in a cannabis plant believed to have mental and physical effects on users. Delta-9-tetrahydrocannabinol is the most psychoactive chemical in the cannabis plant. Urine drug screens are designed to detect 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) and other metabolites of THC.

The substance THC has high lipid solubility, resulting in extensive storage of the drug in the lipid compartments of the body. This lipid solubility is associated with slow excretion of the drug and its metabolites into the urine. A single use of marijuana can result in positive urine tests up to 1 week after administration, whereas long-term use can produce positive results in the urine up to 46 days after cessation.¹⁰³

Nonsteroidal anti-inflammatory drugs have been reported to interfere and cause false-positive results for marijuana in EMIT and other assay systems, although conflicting results have been reported among studies. Rollins et al⁴⁶ tested 510 urine samples from patients who received ibuprofen, naproxen, or fenoprofen at therapeutic dosing regimens (one-time and long-term ingestion). Two false-positive results were found in this study, 1 during the short-term ingestion of ibuprofen (1200 mg for 1 day) and the other after long-term use of naproxen. In contrast, Joseph et al¹⁰⁴ tested 14 different NSAIDs and found no interference with the cannabinoid assay. Rollins et al⁴⁶ speculate that NSAIDs interfere with the enzyme on the EMIT tests, leading to false-positive results.

Other agents that have been shown to cross-react with cannabinoid immunoassays include efavirenz^{44,47} and proton pump inhibitors.⁴³ Efavirenz, a nonnucleoside reverse transcriptase inhibitor, has been extensively reported in the literature to cause false-positive results for

THC. Some speculate that the metabolite of efavirenz leads to interference with the antibody complexes in the immunoassay.⁴⁷

Several studies have evaluated the possibility of testing positive for THC via passive inhalation. Perez-Reyes et al¹⁰⁵ evaluated 3 separate scenarios involving UDS and passive exposure to THC. Methods included (1) placing nonsmokers in a room with participants actively smoking marijuana cigarettes for 1 hour (2.5% THC), (2) placing nonsmokers in a medium-sized station wagon for 1 hour after 4 participants smoked marijuana cigarettes (2.8% THC), and (3) placing nonsmokers in a room with 4 smokers who smoked only 1 marijuana cigarette each. Of the 80 urine samples collected from 12 nonsmokers in the 24 hours after exposure to marijuana, only 2 had THC concentrations greater than 20 ng/mL. No samples met the required 50 ng/mL cutoff concentration mandated by the DHHS; thus, it is highly unlikely for an individual to test positive (50 ng/mL) for THC by urine immunoassay through passive exposure.

Researchers have evaluated whether hemp-containing foods (eg, hemp-seed tea, hemp-seed oil) can produce positive results from UDSs for marijuana. A study evaluating the consumption of a single drink of hemp-seed tea (12-24 oz; to convert to milliliters, multiply by 30) resulted in trace amounts of cannabinoids in the urine; however, none of the urine concentrations met the cutoff concentrations for both EMIT and GC-MS tests.⁴⁸ Several case reports have shown positive results for cannabinoids with the consumption of hemp-seed oil. One study found positive results on RIA after a daily THC dose of 0.6 mg via hemp-seed oil; however, this specimen did not meet the cutoff value for GC-MS.⁴⁵

People using THC often attempt to manipulate the urine to produce negative results. Addition of Visine eyedrops to urine samples has been shown to cause false-negative results for THC.¹⁰⁶ Chemical analysis of Visine eyedrops has shown that the ingredients, benzalkonium chloride and the borate buffer, can directly decrease the concentration of 9-carboxy-THC in the urine with no effects on the antibodies in the immunoassay. However, these ingredients do not chemically alter 9-carboxy-THC, which will still be detected by GC-MS.¹⁰⁶

COCAINE

Cocaine and amphetamines stimulate the central nervous system and are abused primarily for their euphoric effect. In addition, they are frequently used to increase attention and decrease appetite and sleep time. Immunoassay screens are most commonly used in clinical practice to detect cocaine intake.

Urine drug screens used to evaluate cocaine ingestion assess the presence or absence of cocaine's main metabo-

TABLE 4. Classification of Opioids

Derivation	Opioid
From opium	Opium, morphine, codeine, thebaine
Semisynthetic	Heroin, hydrocodone, hydromorphone, oxycodone
Synthetic	Methadone, propoxyphene, meperidine, fentanyl

Data from reference 7.

lite, benzoylecgonine. Cross-reactivity between this screen and substances other than cocaine are nearly nonexistent.^{15,107} Urine screens for cocaine are very accurate in detecting recent cocaine ingestion. Consumption of tea and other natural products created with coca plant leaves produces positive cocaine screen results.^{50,51} Foodstuffs obtained through the Internet and other sources, and adulterated natural products, could also produce a positive result from a cocaine screen even when the person tested denies use of cocaine. In addition, children exposed to cocaine smoke in heavily contaminated environments can have positive cocaine screen results even if they had not intended to ingest the substance.⁴⁹

OPIOIDS

Opioids are a class of drugs comprising both prescribed and illicit agents. Morphine and codeine are naturally occurring alkaloids from the opium poppy seed, *Papaver somniferum*. Table 4⁷ categorizes opioid compounds according to sources of derivation. Opioids can have varying therapeutic effects, such as analgesic, antitussive, and anti-diarrheal properties.

Urinalysis testing for opiates, whether prescribed or illicit, generally detects the metabolite of heroin and codeine, namely morphine. Morphine is further metabolized to 2 main substances, 3-morphine-glucuronide and 6-morphine-glucuronide. The 3-morphine-glucuronide metabolite accounts for 50% of the morphine that is excreted renally and can produce hyperalgesia and neurotoxicity. Fentanyl is usually not detected in urine screens because of lack of metabolites, and oxycodone is not usually detected because of its derivation from thebaine (a compound that is not detected in the urine).¹⁰⁸ Codeine is extensively metabolized, and 10% to 15% of the dose is converted to morphine and norcodeine. All 3 compounds are detected in the urine after ingestion.

Whereas prescribed opiates have indications for pain management, illicit agents or semisynthetic derivatives of morphine are not used for therapeutic effects because of their high abuse potential. Heroin (diacetylmorphine) is a semisynthetic derivative of morphine that is more potent than morphine with rapid onset of action. Heroin also binds to the opioid receptor as an agonist (μ , κ , δ) and inhibits substance P. Further, heroin has effects similar to those of

prescribed opiates, such as sedation, miosis, nausea or vomiting, and decreased blood pressure, heart rate, and respiratory rate. Although detection of actual heroin would be ideal, it is difficult to accomplish because heroin is rapidly metabolized to 6-monoacetylmorphine (6-MAM), morphine, and morphine glucuronide. Heroin can be detected in the serum 3 to 5 minutes after administration, and the metabolite, morphine, can be detected 2 to 4 days after heroin use. Confirmation by GC-MS is necessary for suspected heroin use, and the presence of 6-MAM is confirmatory for heroin. The 6-MAM metabolite is a product of heroin, not morphine or codeine, which makes it ideal for confirmatory testing of heroin. Unfortunately, the metabolite has a short half-life of 36 minutes and is detected in the urine only up to 8 hours after heroin use.^{109,110} A potential problem can arise when street heroin is contaminated with acetylcodeine, which is further metabolized to codeine.²⁰ It can be difficult to differentiate between heroin, codeine, or morphine use among patients with low morphine and codeine concentrations.¹¹¹ Ingestion of products that contain codeine, such as cough medicines and medications for diarrhea, must also be ruled out before determining abuse.

Opiate screening cutoff levels for DHHS were changed from 300 ng/mL to 2000 ng/mL of morphine in December 1998 to avoid false-positive results from poppy-seed ingestion. However, the sensitivity for detecting true opiate use can be a concern,¹¹² and most clinical laboratories continue to use the lower cutoff.⁵³ Positive results for heroin abuse are caused by use of prescribed opiates, such as codeine and hydrocodone; however, ingestion of modest amounts of poppy seeds has been known to cause a positive result from urinalysis. Ingestion of poppy-seed cookies (containing about 1 teaspoon of poppy-seed filling available commercially in the United States for baking) produced positive results for opiates within 2 hours of ingestion among 5 patients.⁶² Codeine was also found in a concentration of 20 ng/mL in 2 samples 2 hours after ingestion. Urine samples analyzed after 24 hours were negative for opiates. Similar results were seen in another analysis in which consumption of poppy-seed bagels produced positive results for codeine and morphine up to 25 hours after ingestion.⁶⁰ A single bagel was estimated to contain 1.5 mg of morphine and 0.1 mg of codeine. Similar results were observed in other analyses with slight variations ranging from 1 hour for earliest detection of morphine to 60 hours for the latest detection.²⁰

Rifampin and rifampicin have also been known to interfere with opiate immunoassays.^{55-57,61} In one case report involving 3 patients, the 1-step chromatographic assay produced false-positive results when urine samples were tested 1 hour after rifampin administration. All 3 samples were negative by urinalysis using the competitive binding

immunoassays and GC-MS. The interference occurred in concentrations as low as 0.05 mg/L. Rifampicin was shown to cause false-positive results in 2 reports^{56,57} and has 12% cross-reactivity. A single oral dose of 600 mg of rifampicin has been detected within 18 hours after ingestion (about 24 hours among patients with renal dysfunction or dehydration).⁵⁶ The color of the drug was not shown to interfere with the reaction. Quinolones also have been known to cause false-positive results on urine screens for opiates.^{53,59}

Methadone is a long-acting opioid that is used as substitution treatment for opioid dependence and chronic pain. Assays for methadone are specific and detect the parent compound because about a third of the drug is excreted unchanged. In patients with maintenance doses of methadone, the urine concentrations for methadone and its metabolite (2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine) range from 1 to 50 mg/L.⁵⁴ A confirmatory testing for methadone use, if suspected, is recommended. Although many urinalysis panels do not routinely screen for methadone, verapamil metabolites that contribute to false-positive results for methadone have been reported.⁵⁸

PHENCYCLIDINE

Phencyclidine is an anesthetic that is abused for its hallucinogenic properties and is often referred to as *angel dust*. This noncompetitive *N*-methyl-D-aspartic acid antagonist inhibits the reuptake of dopamine. Its short-term effects can range from dissociation, euphoria, sensory deprivation, decreased inhibition, increased blood pressure and temperature, and agitation to loss of appetite. In overdose situations, PCP ingestion can result in combativeness or convulsions and can even lead to coma. The psychedelic effects are seen for approximately 1 hour after ingestion, and long-term use can lead to symptoms resembling psychotic disorders, such as schizophrenia. The detection time after smoking PCP is 5 to 15 minutes in the serum²⁰ and approximately 8 days in the urine.⁶⁷ Blood concentrations ranging from 20 to 30 ng/mL can produce excitation, and seizures and death can occur at levels above 100 ng/mL.³ Detection of true PCP use is rare because the drug is no longer widely available in the United States.

In one case report of 3 patients, venlafaxine resulted in false-positive results from urine assays for PCP.⁷⁰ The urine samples were collected from 3 patients in the emergency department, none of whom had a history of PCP use. Venlafaxine was the only medication ingested by all 3 patients. On repeated testing with gas chromatography, the samples produced negative results for PCP. Pure samples of venlafaxine and the metabolite *O*-desmethylvenlafaxine were tested using the emergency department's urine assay test, and again, a positive PCP result was observed. The drug had a cross-reactivity of 0.0125% and the metabolite

of 0.025%. Some speculated that, despite the low cross-reactivity, the combined concentrations of the parent drug and metabolite could have contributed to the false-positive results.

Phencyclidine is not structurally related to venlafaxine; however, on the basis of other false-positive results with drugs of equally dissimilar structure, the potential risk must be considered. This finding was confirmed by another report, in which a false-positive result for PCP was detected in a developmentally disabled patient who received 75 mg/d of venlafaxine XR.⁶⁶ In another report, venlafaxine overdose resulted in a false-positive result for PCP.⁶⁵ Other cross-reactivities for PCP are listed in Table 3.

TRICYCLIC ANTIDEPRESSANTS

Although assays for drugs of abuse do not routinely test for TCAs, rapid screening for TCA in the urine is often valuable in emergency situations, such as intentional overdose or toxicity. Results of urine screening for TCA have an important role in determining early management of patients; however, many commonly prescribed and over-the-counter medications can lead to false-positive results from TCA assays.

The 3-ring nucleus of TCAs is the characteristic structure of this class of antidepressants. Several structurally related medications (ie, 3-ringed structures) have been shown to cross-react with TCAs in either serum or urine immunoassays. Antihistamine agents (eg, cyproheptadine,^{80,81} carbamazepine,^{72,74,75} cyclobenzaprine,⁷⁹ and quetiapine^{71,76,77}) have often been reported to interfere with the serum immunoassay for TCAs because of their 3-ringed structures. Although structurally dissimilar to TCAs, the antihistamines diphenhydramine,⁷⁸ hydroxyzine,⁷³ and cetirizine⁷³ (hydroxyzine's metabolite) have also been shown to interfere with serum TCA immunoassay in overdose situations. Unfortunately, these case reports did not test for interference in the urine immunoassay, except for quetiapine and cyclobenzaprine.

CONCLUSION

Urine drug screens are valuable tools in health care, the workplace, and other settings. Accurate interpretation of the validity and reliability of these tools is critical for making decisions that will ultimately have social and legal ramifications. Understanding how to evaluate UDSs for adulterations, substitutions, and potential false-positive results is complex but vital to interpret these results. A detailed medication history, including prescription, nonprescription, and herbal medications, and proper knowledge of medications that cross-react with UDSs are essential.

Clinicians need to be aware that the preliminary tests performed by immunoassays are presumptive only and that external factors and variables can influence these results. A confirmatory test (eg, GC-MS) is required before decisions can be made on the basis of UDSs. Also, UDSs do not provide information regarding the length of time since last ingestion, overall duration of abuse, or state of intoxication.

Thus, it is important that health care professionals understand the limitations of UDSs and appropriately assess results using both objective and clinical information. Inaccurate interpretations of these tools can have serious consequences and should be minimized.

REFERENCES

1. Tests for drugs of abuse. *Med Lett Drugs Ther.* 2002;44(1137):71-73.
2. Armbruster DA, Schwarzhoff RH, Hubster EC, Liserio MK. Enzyme immunoassay, kinetic microparticle immunoassay, radioimmunoassay, and fluorescence polarization immunoassay compared for drugs-of-abuse screening. *Clin Chem.* 1993;39(10):2137-2146.
3. Fenton JJ. *Toxicology: A Case-Oriented Approach.* Boca Raton, FL: CRC Press; 2002:359-402.
4. Sloop G, Hall M, Simmons GT, Robinson CA. False-positive postmortem EMIT drugs-of-abuse assay due to lactate dehydrogenase and lactate in urine. *J Anal Toxicol.* 1995;19(7):554-556.
5. US Department of Health and Human Services. Mandatory guidelines and proposed revisions to mandatory guidelines for federal workplace drug testing programs: notices. *Federal Register.* April 13, 2004;69(71):19659-19660. <http://ncadistore.samhsa.gov/catalog/ProductDetails.aspx?ProductID=16833>. Accessed November 30, 2007.
6. Luzzi VI, Saunders AN, Koenig JW, et al. Analytic performance of immunoassays for drugs of abuse below established cutoff values. *Clin Chem.* 2004 Apr;50(4):717-722. Epub 2004 Feb 5.
7. Inaba DS, Cohen WE. *Uppers, Downers, All Arounder: Physical and Mental Effects of Psychoactive Drugs.* 5th ed. Ashland, OR: CNS Publications, Inc; 2004.
8. Woelfel JA. Drug abuse urine tests: false-positive results. *Pharmacist Lett/Prescribers Lett.* 2005;21(3):210-314.
9. Council on Scientific Affairs. Scientific issues in drug testing. *JAMA.* 1987;257(22):3110-3114.
10. Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage.* 2004;27(3):260-267.
11. Rosse RB, Deutsch LH, Deutsch SI. Medical assessment and laboratory testing in psychiatry. In: Sadock BJ, Sadock VA, eds. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry.* Vol 1. 7th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2000:732-755.
12. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monit.* 2004;26(2):200-205.
13. Warner A. Interference of common household chemicals in immunoassay methods for drugs of abuse [published correction appears in *Clin Chem.* 1989;35(11):2257]. *Clin Chem.* 1989;35(4):648-651.
14. Jaffee WB, Trucco E, Levy S, Weiss RD. Is this urine really negative? A systematic review of tampering methods in urine drug screening and testing. *J Subst Abuse Treat.* 2007 Jul;33(1):33-42. Epub 2007 Jan 16.
15. Eskridge KD, Guthrie SK. Clinical issues associated with urine testing of substances of abuse. *Pharmacotherapy.* 1997;17(3):497-510.
16. Casavant MJ. Urine drug screening in adolescents. *Pediatr Clin North Am.* 2002;49(2):317-327.
17. Hammett-Stabler CA, Pesce AJ, Cannon DJ. Urine drug screening in the medical setting. *Clin Chim Acta.* 2002;315(1-2):125-135.
18. Dasgupta A, Chughtai O, Hannah C, Davis B, Wells A. Comparison of spot tests with AdultaCheck 6 and Intect 7 urine test strips for detecting the presence of adulterants in urine specimens. *Clin Chim Acta.* 2004;348(1-2):19-25.
19. Peace MR, Tarnai LD. Performance evaluation of three on-site adulterant detection devices for urine specimens. *J Anal Toxicol.* 2002;26(7):464-470.
20. Hawks RI, Chaign CN, eds. *Urine Testing for Drugs of Abuse.* Rockville, MD: Department of Health and Human Services, National Institute on Drug Abuse; 1986. National Institute on Drug Abuse Research Monograph Series, No. 73. <http://www.nida.nih.gov/pdf/monographs/73.pdf>. Accessed November 30, 2007.
21. Cody JT. Precursor medications as a source of methamphetamine and/or amphetamine positive drug testing results. *J Occup Environ Med.* 2002;44(5):435-450.
22. Colbert DL. Possible explanation for trimethobenzamide cross-reaction in immunoassays of amphetamine/methamphetamine [letter]. *Clin Chem.* 1994;40(6):948-949.
23. Gilbert RB, Peng PI, Wong D. A labetalol metabolite with analytical characteristics resembling amphetamines. *J Anal Toxicol.* 1995;19(2):84-86.
24. Grinstead GF. Ranitidine and high concentrations of phenylpropranolamine cross react in the EMIT monoclonal amphetamine/methamphetamine assay. *Clin Chem.* 1989;35(9):1998-1999.
25. Jones R, Klette K, Kuhlman JJ, et al. Trimethobenzamide cross-reacts in immunoassays of amphetamine/methamphetamine [letter]. *Clin Chem.* 1993;39(6):699-700.
26. Kelly KL. Ranitidine cross-reactivity in the EMIT d.a.u. Monoclonal Amphetamine/Methamphetamine Assay [letter]. *Clin Chem.* 1990;36(9):1391-1392.
27. Levine BS, Caplan YH. Isometheptene cross reacts in the EMIT amphetamine assay. *Clin Chem.* 1987;33(7):1264-1265.
28. Manzi S, Law T, Shannon MW. Methylphenidate produces a false-positive urine amphetamine screen [letter]. *Pediatr Emerg Care.* 2002;18(5):401.
29. Melanson SE, Lee-Lewandrowski E, Griggs DA, Long WH, Flood JG. Reduced interference by phenothiazines in amphetamine drug of abuse immunoassays. *Arch Pathol Lab Med.* 2006;130(12):1834-1838.
30. Merigian KS, Browning R, Kellerman A. Doxepin causing false-positive urine test for amphetamine [letter]. *Ann Emerg Med.* 1993;22(8):1370.
31. Merigian KS, Browning RG. Desipramine and amantadine causing false-positive urine test for amphetamine [letter]. *Ann Emerg Med.* 1993;22(12):1927-1928.
32. Nice A, Maturen A. False-positive urine amphetamine screen with ritodrine. *Clin Chem.* 1989;35(7):1542-1543.
33. Nixon AL, Long WH, Puopolo PR, Flood JG. Bupropion metabolites produce false-positive urine amphetamine results [letter]. *Clin Chem.* 1995;41(6)(pt 1):955-956.
34. Olsen KM, Gulliksen M, Christophersen AS. Metabolites of chlorpromazine and brompheniramine may cause false-positive urine amphetamine results with monoclonal EMIT d.a.u. immunoassay [letter]. *Clin Chem.* 1992;38(4):611-612.
35. Poklis A, Hall KV, Still J, Binder SR. Ranitidine interference with the monoclonal EMIT d.a.u. amphetamine/methamphetamine immunoassay. *J Anal Toxicol.* 1991;15(2):101-103.
36. Poklis A, Moore KA. Response of EMIT amphetamine immunoassays to urinary desoxyephedrine following Vicks inhaler use. *Ther Drug Monit.* 1995;17(1):89-94.
37. Roberge RJ, Luellen JR, Reed S. False-positive amphetamine screen following a trazodone overdose [letter]. *J Toxicol Clin Toxicol.* 2001;39(2):181-182.
38. Romberg RW, Needleman SB, Snyder JJ, Greedan A. Methamphetamine and amphetamine derived from the metabolism of selegiline. *J Forensic Sci.* 1995;40(6):1100-1102.
39. Stout PR, Klette KL, Horn CK. Evaluation of ephedrine, pseudoephedrine and phenylpropranolamine concentrations in human urine samples and a comparison of the specificity of DRI amphetamines and Abuscreen online (KIMS) amphetamines screening immunoassays. *J Forensic Sci.* 2004;49(1):160-164.
40. Weintraub D, Linder MW. Amphetamine positive toxicology screen secondary to bupropion. *Depress Anxiety.* 2000;12(1):53-54.
41. Fraser AD, Howell P. Oxaprozin cross-reactivity in three commercial immunoassays for benzodiazepines in urine. *J Anal Toxicol.* 1998;22(1):50-54.
42. Pulini M. False-positive benzodiazepine urine test due to oxaprozin [letter]. *JAMA.* 1995;273(24):1905-1906.

43. Protonix [package insert]. Philadelphia, PA: Wyeth; 2007.
44. la Porte CJ, Droste JA, Burger DM. False-positive results in urine drug screening in healthy volunteers participating in phase I studies with efavirenz and rifampin [letter]. *Ther Drug Monit*. 2006;28(2):286.
45. Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the impact of hemp food consumption on workplace drug tests. *J Anal Toxicol*. 2001;25(8):691-698.
46. Rollins DE, Jennison TA, Jones G. Investigation of interference by nonsteroidal anti-inflammatory drugs in urine tests for abused drugs. *Clin Chem*. 1990;36(4):602-606.
47. Rossi S, Yaksh T, Bentley H, van den Brande G, Grant I, Ellis R. Characterization of interference with 6 commercial delta9-tetrahydrocannabinol immunoassays by efavirenz (glucuronide) in urine [letter]. *Clin Chem*. 2006;52(5):896-897.
48. Steinagle GC, Upfal M. Concentration of marijuana metabolites in the urine after ingestion of hemp seed tea. *J Occup Environ Med*. 1999;41(6):510-513.
49. De Giorgio F, Rossi SS, Rainio J, Chiarotti M. Cocaine found in a child's hair due to environmental exposure? *Int J Legal Med*. 2004;118(5):310-312.
50. Hickey K, Seliem R, Shields J, McKee A, Nichols JH. A positive drug test in the pain management patient: deception or herbal cross-reactivity? *Clin Chem*. 2002;48(6)(pt 1):958-960.
51. Mazor SS, Mycyk MB, Wills BK, Brace LD, Gussow L, Erickson T. Coca tea consumption causes positive urine cocaine assay. *Eur J Emerg Med*. 2006;13(6):340-341.
52. O'Neil MJ, Smith A, Heckelman PE, eds. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*. 13th ed. Whitehouse Station, NJ: Merck Research Laboratories; 2001.
53. Baden LR, Horowitz G, Jacoby H, Eliopoulos GM. Quinolones and false-positive urine screening for opiates by immunoassay technology. *JAMA*. 2001;286(24):3115-3119.
54. Baselt RC, Casarett LJ. Urinary excretion of methadone in man. *Clin Pharmacol Ther*. 1972;13(1):64-70.
55. Daher R, Haidar JH, Al-Amin H. Rifampin interference with opiate immunoassays [letter]. *Clin Chem*. 2002;48(1):203-204.
56. de Paula M, Saiz LC, Gonzalez-Revalderia J, Pascual T, Alberola C, Miravalles E. Rifampicin causes false-positive immunoassay results for urine opiates. *Clin Chem Lab Med*. 1998;36(4):241-243.
57. Herrera Trevilla P, Ortiz Jimenez E, Tena T, Lora Tamayo C. Presence of rifampicin in urine causes cross-reactivity with opiates using the KIMS method [letter]. *J Anal Toxicol*. 1995;19(3):200.
58. Lichtenwalner MR, Mencken T, Tully R, Petosa M. False-positive immunochemical screen for methadone attributable to metabolites of verapamil. *Clin Chem*. 1998;44(5):1039-1041.
59. Meatherall R, Dai J. False-positive EMIT II opiates from ofloxacin. *Ther Drug Monit*. 1997;19(1):98-99.
60. Struempfer RE. Excretion of codeine and morphine following ingestion of poppy seeds. *J Anal Toxicol*. 1987;11(3):97-99.
61. van As H, Stolk LM. Rifampicin cross-reacts with opiate immunoassay [letter]. *J Anal Toxicol*. 1999;23(1):71.
62. Zebelman AM, Troyer BL, Randall GL, Batjer JD. Detection of morphine and codeine following consumption of poppy seeds [letter]. *J Anal Toxicol*. 1987;11(3):131-132.
63. Vincent EC, Zebelman A, Goodwin C, Stephens MM. What common substances can cause false positives on urine screens for drugs of abuse? *J Fam Pract*. 2006;55(10):893-894, 897.
64. Baselt RC. *Disposition of Toxic Drugs and Chemicals in Man*. 5th ed. Foster City, CA: Chemical Toxicology Institute; 2000.
65. Bond GR, Steele PE, Uges DR. Massive venlafaxine overdose resulted in a false positive Abbott AxSYM urine immunoassay for phencyclidine. *J Toxicol Clin Toxicol*. 2003;41(7):999-1002.
66. Brahm NC, Brown RC. Venlafaxine usage resulted in a false positive immunoassay for phencyclidine. *J Coll Psychiatr Neurol Pharm*. 2006. http://cpnp.org/_docs/news/20070115.pdf. Accessed December 3, 2007.
67. Gupta RC, Lu I, Oei GL, Lundberg GD. Determination of phencyclidine (PCP) in urine and illicit street drug samples. *Clin Toxicol*. 1975;8(6):611-621.
68. Hull MJ, Griggs D, Knoepp SM, Smogorzewska A, Nixon A, Flood JG. Postmortem urine immunoassay showing false-positive phencyclidine reactivity in a case of fatal tramadol overdose. *Am J Forensic Med Pathol*. 2006;27(4):359-362.
69. Khajawall AM, Simpson GM. Critical interpretation of urinary phencyclidine monitoring. *Adv Alcohol Subst Abuse*. 1984 Spring;3(3):65-73.
70. Sena SF, Kazimi S, Wu AH. False-positive phencyclidine immunoassay results caused by venlafaxine and O-desmethylvenlafaxine [letter]. *Clin Chem*. 2002;48(4):676-677.
71. Al-Mateen CS, Wolf CE II. Falsely elevated imipramine levels in a patient taking quetiapine [letter]. *J Am Acad Child Adolesc Psychiatry*. 2002;41(1):5-6.
72. Chattergoon DS, Verjee Z, Anderson M, et al. Carbamazepine interference with an immune assay for tricyclic antidepressants in plasma. *J Toxicol Clin Toxicol*. 1998;36(1-2):109-113.
73. Dasgupta A, Wells A, Datta P. False-positive serum tricyclic antidepressant concentrations using fluorescence polarization immunoassay due to the presence of hydroxyzine and cetirizine. *Ther Drug Monit*. 2007;29(1):134-139.
74. Fleischman A, Chiang VW. Carbamazepine overdose recognized by a tricyclic antidepressant assay. *Pediatrics*. 2001;107(1):176-177.
75. Matos ME, Burns MM, Shannon MW. False-positive tricyclic antidepressant drug screen results leading to the diagnosis of carbamazepine intoxication. *Pediatrics*. 2000;105(5):E66.
76. Schussler JM, Juenke JM, Schussler I. Quetiapine and falsely elevated nortriptyline level [letter]. *Am J Psychiatry*. 2003;160(3):589.
77. Sloan KL, Haver VM, Saxon AJ. Quetiapine and false-positive urine drug testing for tricyclic antidepressants [letter]. *Am J Psychiatry*. 2000;157(1):148-149.
78. Sorisky A, Watson DC. Positive diphenhydramine interference in the EMIT-st assay for tricyclic antidepressants in serum [letter]. *Clin Chem*. 1986;32(4):715.
79. Van Hoey NM. Effect of cyclobenzaprine on tricyclic antidepressant assays. *Ann Pharmacother*. 2005 Jul-Aug;39(7-8):1314-1317. Epub 2005 Jun 14.
80. Wians FH Jr, Norton JT, Wirebaugh SR. False-positive serum tricyclic antidepressant screen with cyproheptadine [letter]. *Clin Chem*. 1993;39(6):1355-1356.
81. Yuan CM, Spandorfer PR, Miller SL, Henretig FM, Shaw LM. Evaluation of tricyclic antidepressant false positivity in a pediatric case of cyproheptadine (peractin) overdose. *Ther Drug Monit*. 2003;25(3):299-304.
82. Dietzen DJ, Ecos K, Friedman D, Beason S. Positive predictive values of abused drug immunoassays on the Beckman Synchron in a veteran population. *J Anal Toxicol*. 2001;25(3):174-178.
83. Ferrara SD, Tedeschi L, Frison G, et al. Drugs-of-abuse testing in urine: statistical approach and experimental comparison of immunochemical and chromatographic techniques. *J Anal Toxicol*. 1994;18(5):278-291.
84. Janda I, Alt A. Improvement of ethyl glucuronide determination in human urine and serum samples by solid-phase extraction. *J Chromatogr B Biomed Sci Appl*. 2001;758(2):229-234.
85. Jones AW. Urine as a biological specimen for forensic analysis of alcohol and variability in the urine-to-blood relationship. *Toxicol Rev*. 2006;25(1):15-35.
86. Allen JP, Litten RZ. The role of laboratory tests in alcoholism treatment. *J Subst Abuse Treat*. 2001;20(1):81-85.
87. Hsu J, Liu C, Liu CP, et al. Performance characteristics of selected immunoassays for preliminary test of 3,4-methylenedioxymethamphetamine, methamphetamine, and related drugs in urine specimens. *J Anal Toxicol*. 2003;27(7):471-478.
88. Kunsman GW, Manno JE, Cockerham KR, Manno BR. Application of the Syva EMIT and Abbott TDx amphetamine immunoassays to the detection of 3,4-methylene-dioxymethamphetamine (MDMA) and 3,4-methylenedioxymethamphetamine (MDEA) in urine. *J Anal Toxicol*. 1990;14(3):149-153.
89. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. *Pediatrics*. 1997;100(4):705-708.
90. Perry PJ, Alexander B, Liskow BI, DeVane CL. *Psychotropic Drug Handbook*. 8th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2007.
91. Rothschild AJ, Shindul-Rothschild JA, Viguera A, Murray M, Brewster S. Comparison of the frequency of behavioral disinhibition on alprazolam, clonazepam, or no benzodiazepine in hospitalized psychiatric patients. *J Clin Psychopharmacol*. 2000;20(1):7-11.

92. Uhlenhuth EH, Balter MB, Ban TA, Yang K. International study of expert judgment on therapeutic use of benzodiazepines and other psychotherapeutic medications: IV: therapeutic dose dependence and abuse liability of benzodiazepines in the long-term treatment of anxiety disorders. *J Clin Psychopharmacol*. 1999;19(6)(suppl 2):23S-29S.
93. Green KB, Isenschmid DS. Medical review officer interpretation of urine drug test results. *Forensic Sci Rev*. 1995;7:41-59.
94. Greenblatt DJ, Shader RI. Pharmacokinetics of antianxiety agents. In: Meltzer H, ed. *Psychopharmacology: The Third Generation of Progress*. New York, NY: Raven Press; 1987:1377-1386.
95. Laloup M, Ramirez Fernandez MD, Wood M, et al. Detection of diazepam in urine, hair and preserved oral fluid samples with LC-MS-MS after single and repeated administration of Myolastan and Valium. *Anal Bioanal Chem*. 2007 Aug;388(7):1545-1556. Epub 2007 Apr 28.
96. Concheiro M, Villain M, Bouchet S, Ludes B, Lopez-Rivadulla M, Kintz P. Windows of detection of tetrazepam in urine, oral fluid, beard, and hair, with a special focus on drug-facilitated crimes. *Ther Drug Monit*. 2005;27(5):565-570.
97. Kintz P, Villain M, Ludes B. Testing for the undetectable in drug-facilitated sexual assault using hair analyzed by tandem mass spectrometry as evidence. *Ther Drug Monit*. 2004;26(2):211-214.
98. Pavlic M, Libiseller K, Grubwieser P, Schubert H, Rabl W. Medicolegal aspects of tetrazepam metabolism. *Int J Legal Med*. 2007 May;121(3):169-174. Epub 2006 Oct 5.
99. Daypro [package insert]. New York, NY: GD Searle LLC, Division of Pfizer Inc; 2006.
100. Colbert DL. Drug abuse screening with immunoassays: unexpected cross-reactivities and other pitfalls. *Br J Biomed Sci*. 1994;51(2):136-146.
101. Garretty DJ, Wolff K, Hay AW, Raistrick D. Benzodiazepine misuse by drug addicts. *Ann Clin Biochem*. 1997;34 (pt 1):68-73.
102. Substance Abuse and Mental Health Services Administration (2006). Results from the 2005 National Survey on Drug Use and Health: National Findings. Office of Applied Studies, Department of Health and Human Services: The National Survey on Drug Use and Health Series H-30, No. SMA 06-4194. <http://oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm>. Accessed December 4, 2007.
103. Ellis GM Jr, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther*. 1985;38(5):572-578.
104. Joseph R, Dickerson S, Willis R, Frankenfield D, Cone EJ, Smith DR. Interference by nonsteroidal anti-inflammatory drugs in EMIT and TDx assays for drugs of abuse. *J Anal Toxicol*. 1995;19(1):13-17.
105. Perez-Reyes M, Di Guiseppi S, Mason AP, Davis KH. Passive inhalation of marijuana smoke and urinary excretion of cannabinoids. *Clin Pharmacol Ther*. 1983;34(1):36-41.
106. Pearson SD, Ash KO, Urry FM. Mechanism of false-negative urine cannabinoid immunoassay screens by Visine eyedrops. *Clin Chem*. 1989;35(4):636-638.
107. Leino A, Saarimies J, Gronholm M, Lillsunde P. Comparison of eight commercial on-site screening devices for drugs-of-abuse testing. *Scand J Clin Lab Invest*. 2001;61(4):325-331.
108. OxyContin [package insert]. Stamford, CT: Purdue Pharma LP; 2007.
109. Cone EJ, Dickerson S, Paul BD, Mitchell JM. Forensic drug testing for opiates. V. Urine testing for heroin, morphine, and codeine with commercial opiate immunoassays. *J Anal Toxicol*. 1993;17(3):156-164.
110. Derks HJGM, van Twillert K, Zomer G. Determination of 6-acetylmorphine in urine as a specific marker for heroin abuse by high-performance liquid chromatography with fluorescence detection. *Anal Chim Acta*. 1985;170:13-20.
111. Substance Abuse Testing Committee. Critical issues in urinalysis of abused substances: report of the substance-abuse testing committee. *Clin Chem*. 1988;34(3):605-632.
112. Paul BD, Shimomura ET, Smith ML. A practical approach to determine cutoff concentrations for opiate testing with simultaneous detection of codeine, morphine, and 6-acetylmorphine in urine. *Clin Chem*. 1999;45(4):510-519.