REVIEW

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.

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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 1[5]). 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 2[7-12] 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] Benzoylecgonine.
[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 transpepsidase, 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, anorexiants, 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		Hemp-containing foods
	Benzphetamine		NSAIDs
	Bupropion		Proton pump inhibitors
	Chlorpromazine		Tolmetin
	Clobenzorex[b]	Cocaine[49-51]	Coca leaf tea
	l-Deprenyl[c]		Topical anesthetics containing cocaine
	Desipramine	Opioids, opiates, and heroin[8,16,52-63]	Dextromethorphan
	Dextroamphetamine		Diphenhydramine[e]
	Ephedrine		Heroin
	Fenproporex[b]		Opiates (codeine, hydromorphone, hydrocodone, morphine)
	Isometheptene		Poppy seeds
	Isoxsuprine		Quinine
	Labetalol		Quinolones
	MDMA		Rifampin
	Methamphetamine		Verapamil and metabolites[e]
	l-Methamphetamine (Vick's inhaler)[d]	Phencyclidine[8,52,64-70]	Dextromethorphan
	Methylphenidate		Diphenhydramine[e]
	Phentermine		Doxylamine
	Phenylephrine		Ibuprofen
	Phenylpropanolamine		Imipramine
	Promethazine		Ketamine
	Pseudoephedrine		Meperidine
	Ranitidine		Mesoridazine
	Ritodrine		Thioridazine
	Selegiline		Tramadol
	Thioridazine		Venlafaxine, O-desmethylvenlafaxine
	Trazodone	Tricyclic antidepressants [71-81]	Carbamazepine[f]
	Trimethobenzamide		Cyclobenzaprine
	Trimipramine		Cyproheptadine[f]
Benzodiazepines[16,41,42]	Oxaprozin		Diphenhydramine[f]
	Sertraline		Hydroxyzine[f]
			Quetiapine

[a] MDMA = methylenedioxymethylamphetamine, NSAID = nonsteroidal anti-inflammatory drug.
[b] Approved in Mexico. Not approved in the United States.
[c] Converts to *l*-methamphetamine and *l*-amphetamine.
[d] Newer immunoassays have corrected the false-positive result for Vick's inhaler.
[e] Diphenhydramine and verapamil (including metabolites) have been shown to cause positive results in methadone assays only.
[f] Reports 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 anorexiants 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

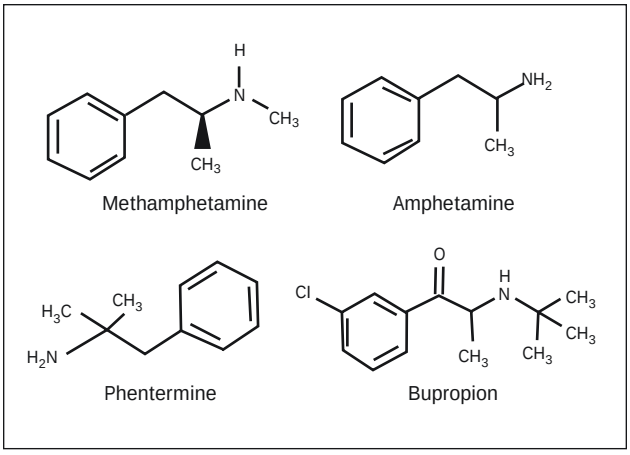

FIGURE. Agents that can cause positive results on amphetamine immunoassay. Adapted from ChemIDplus Lite. US National Library of Medicine, National Institutes of Health. Available from: http://sis.nlm.nih.gov/chemical.html. Accessed December 7, 2007.

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 pharmacologic 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 al[46] 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 al[104] tested 14 different NSAIDs and found no interference with the cannabinoid assay. Rollins et al[46] 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 al[105] 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 4[7] categorizes opioid compounds according to sources of derivation. Opioids can have varying therapeutic effects, such as analgesic, antitussive, and antidiarrheal 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 serum[20] 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 cetirizine[73] (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.

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