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What Can a Urine Drug Screening Immunoassay Really Tell Us?

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Abstract

Urine drug screening has become standard of care in many medical practice settings to assess compliance, detect misuse, and/or to provide basis for medical or legal action. The antibody-based enzymatic immunoassays used for qualitative analysis of urine have significant drawbacks that clinicians are often not aware of. Recent literature suggests that there is a lack of understanding of the shortcomings of these assays by clinicians who are ordering and/or interpreting them. This article addresses the state of each of the individual immunoassays that are most commonly used today in order to help the reader become proficient in the interpretation and application of the results. Some literature already exists regarding sources of "false positives" and "false negatives," but none seem to present the material with the practicing clinician in mind. This review aims to avoid overwhelming the reader with structures and analytical chemistry. The reader will be presented relevant clinical knowledge that will facilitate appropriate interpretation of immunoassays regardless of practice settings. Using this review as a learning tool and a reference, clinicians will be able to interpret the results of commonly used immunoassays in an evidence-based, informed manner and minimize the negative impact that misinterpretation has on patient care.

Keywords

immunoassay, urine drug screen, false positive, false negative

Introduction

The use of rapid urine drug screens in many areas of medicine has substantially increased in recent years.[1] The implementation of these screens into practice has expanded to emergency departments, primary care clinics, mental health facilities, pain management centers, among others.[2] Despite the convenience of these assays, the limitations of the detection methods are many and must be understood by all clinicians, especially those who are ordering and/or interpreting the results so that the resulting actions are indicated and supported. Currently, enzymatic immunoassays (EIAs) are the standard for rapid urine toxicology screening but many of the EIAs lack specificity and/or sensitivity for the compounds they are designed to detect and are plagued by inappropriate results.[3,4] These assays are also limited to detecting drugs that can achieve detectable concentrations in the urine.[5]

Immunoassays rely on the intrinsic ability of the developed antibody to bind to the unique 3-dimensional structure of a molecule or class of molecules.[2] Unfortunately, many therapeutic agents used in practice today share structural similarities that make it difficult for the antibody-based assay to only detect its target compound or class of compounds. With that, there are many classes of therapeutic agents in which the individual drugs within the class have very dissimilar structures, making it difficult to develop a single antibody to detect all members of any particular class, potentially leading to inappropriate results.

Due to the prevalence of ambiguous results, patients whose urine exceeds certain threshold values for selected classes of commonly abused substances should always be sent for further evaluation, also referred to as ''confirmatory testing,'' by more advanced, analytical, and quantitative methods of detection such as gas chromatography, liquid chromatography, and/or mass spectrometry. Unfortunately, quantitative testing via these analytical methods takes more time than the rapid immunoassay, is more expensive to the healthcare system, requires expertise to perform, and may require documentation of a previous positive qualitative assay, such as an EIA, prior to approval.[1,3] In fact, at many smaller community institutions, this type of confirmatory testing isn't available. The urine samples would then need to be sent to an outside laboratory, which

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could present another potential source of inappropriate results in that the chain of custody is trusted with handling the samples properly, delivering them in a timely manner, and preventing adulteration. Smaller institutions may also opt to forego sending of the samples due to the time it takes to get results and/or cost. Furthermore, even the gold standard of confirmatory testing, gas chromatography/mass spectrometry (GC/MS), can fail to identify certain substances of interest.[1,6] As biotechnology and qualitative detection methods improve, more specific and sensitive tests may be developed. However, in our current state of practice, all clinicians must be aware of the shortcomings of the EIAs and be able to effectively apply the results of rapid urine drug screens to their patients' unique scenarios.

Because of the inadequacies of the current urine drug immunoassays, clinicians should rely more on their professional training than the presumptive results of an immunoassay to make real-time clinical decisions as subsequent pharmacological or nonpharmacological treatment could potentially cause patient harm. More specifically, knowledge of specific toxidromes, a certain set of symptoms that are suggestive of toxicity of a particular class of substances, along with the physical evaluation of the patient, and assessment of the unique clinical scenario should take precedence to the results of rapid urine drug screens and should be the basis of clinical decision making.

The goal of this article is not to overwhelm the reader with structures and analytical chemistry, but instead to provide a collection of relevant clinical knowledge that will benefit and assist the reader in accurately interpreting urine drug immunoassay results in their respective practice settings.

Where the Immunnoassays Fall Short

Amphetamines

The increasing popularity of amphetamine use in academic settings and throughout the community for both legitimate medical reasons and for recreational purposes necessitates the development and use of a rapid drug screen for this class of compounds. Most EIAs for amphetamines are designed to detect D-amphetamine and D-methamphetamine. Regrettably, the EIAs for these compounds have been plagued by inappropriate positive results due to a lack of specificity for many agents within this class and due to other classes of therapeutic agents that share the same phenethylamine base structure.[2] Another noteworthy issue with some amphetamine immunoassays is the lack of sensitivity to detect designer drugs such as 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyamphetamine (MDMA, ''ecstasy,'' or ''molly'') that have found a following in the rave scene.[1,2,7] Some data suggest that the sensitivity of detecting MDMA is about 50% less than D-amphetamine and D-methamphetamine for most urine EIAs which supports the use of an adjunctive MDMA immunoassay if misuse is suspected.[1,2,7] Furthermore, with the explosion in popularity of the phenethylamine-based ''bath salts'' and ''2C'' drugs (marketed as ''plant food'' and/or labeled as ''not for human consumption'')[8] and their modest structural similarities to other amphetamines, one might assume that they would be detected on urine amphetamine immunoassay. Unfortunately, currently used EIAs for amphetamines lack ideal cross reactivity for this emerging collection of compounds, and bath salts, and 2C compounds are not commonly detected in the urine via the amphetamine immunoassays.[9,10]

Barbiturates

Therapeutic use of barbiturates has plummeted with the development of safer and more available sedative hypnotics and anxiolytics such as the benzodiazepines and the nonbenzodiazepine ''Z-drugs'' (zolpidem, zaleplon, and eszopiclone).[11] However, the immunoassay for barbiturates produces reliable results, especially when compared to some of the other routinely used immunoassays. The barbiturate immunoassay antibody typically targets secobarbital but displays good sensitivity and specificity for other members of the barbiturate class.[2] Inappropriately positive or negative results are rare due to the conserved barbituric acid moiety common to the different individual agents within the barbiturate class.[12]

Benzodiazepines

There are 2 main reasons why most urine immunoassays for benzodiazepines will not reliably provide accurate results. First, most EIAs are designed to detect nordiazepam or oxazepam, which are direct metabolites of diazepam.[13] Many of the most commonly prescribed and most frequently abused benzodiazepines, including alprazolam, lorazepam, and clonazepam, do not share these metabolites[5] and thus can often go undetected on many urine drug immunoassays. Second, some prescribed benzodiazepines, especially clonazepam, at therapeutic and even supratherapeutic doses may not exceed detection threshold levels in the urine and simply go undetected.[5] Some of the newer generation EIAs are able to detect alprazolam more reliably, but midazolam, lorazepam, and clonazepam continue to have exceedingly low detection rates.[14] As one may expect, the extensive use of this class of medications as anticonvulsants, skeletal muscle relaxants, anxiolytics, sedatives, hypnotics, and antiemetics makes differentiating routine therapeutic use from misuse difficult using only an immunoassay.

Cocaine

The immunoassay for cocaine (''coke'' and ''snow'') actually detects the presence of the major, inactive metabolite excreted in the urine, benzoylecgonine (BE). The antibody used to detect BE in the urine demonstrates good sensitivity and specificity for its target.[2] Passive inhalation of crack cocaine will typically not produce a positive result except in the case of prolonged exposure to cocaine smoke in a heavily contaminated

environment.[15] Despite the assay's ability to reliably detect BE, there exists a few clinical situations in which the EIA may fail to appropriately determine the extent of cocaine use.[2] First, in the case of an acute, massive overdose of cocaine, metabolism may take longer and thus, the time to a concentration of BE in the urine capable of exceeding the detection threshold is extended due to saturation of the metabolism enzyme. Depending on the time of presentation to the medical facility, concentrations of BE may be too low in the urine, not surpass the detection threshold, and go undetected. There is at least 1 case report of this occurrence.[16] Second, certain teas including coca tea and some preparations of yerba mate that contain part of the coca plant, native to Latin America and common within the Hispanic population, may produce positive results and could be incorrectly interpreted as cocaine abuse.[17]

Opioid Series—Opiates

The traditional opioid immunoassay, more appropriately called the opiate immunoassay, may be the most controversial and least specific and sensitive urine drug screen available today. The antibodies used in the opiate assay target the natural alkaloids including morphine and codeine, which are extracted directly from the opium poppy *Papaver somniferum*.[18] As more modifications are made to the chemical structure of these natural compounds (for example, breaking of "The Morphine Rule"), it will be more difficult to detect these modified compounds via the opiate urine immunoassay. Although the structure is slightly modified, diacetylmorphine (heroin) is synthesized directly from morphine and its presence is often detected using the traditional opiate immunoassay.[3,19] However, some of the most abused prescription narcotics including methadone, oxycodone, and tramadol are some of the most frequently undetected due to their more synthetic nature.[20,21] Some newer generation opiate immunoassays are capable of detecting some of the semisynthetics such as hydrocodone and hydromorphone, but the other more synthetic opioids require adjunctive immunoassays in order to detect their presence in urine.[21] The more specific assays typically only have the specificity to detect 1 or 2 desired compounds and can feature problematic cross reactivity as well (see Appendix A). This article also contains sections for the specific adjunctive immunoassays for the semisynthetic and fully synthetic opioids as well.

Opioid Series—Oxycodone

Oxycodone is a semisynthetic opioid typically reserved for patients with moderate to severe pain due to its high tolerability.[88] It has analgesic potency similar to morphine but has fewer side effects and has become one of the most addictive opioids on the market today.[1] Due to its structural dissimilarity to morphine and codeine, oxycodone is not reliably detected using the traditional opiate assay.[2,18] The adjunctive oxycodone immunoassay features very high sensitivity and specificity for oxycodone and will only detect oxycodone and oxymorphone (both a metabolite of oxycodone and available commercially as the single entity in Opana® ER) with almost zero cross reactivity with other opioid analgesics.[1,88]

Opioid Series—Methadone

Methadone is a fully synthetic opioid with the *R* isomer exhibiting strong mu receptor agonist activity and the *S* isomer exhibiting weak NMDA receptor antagonism. It is often dosed multiple times a day for severe pain requiring around the clock management or once daily for maintenance therapy in opioid dependency and detoxification.[89] As with the other more synthetic opioids, methadone goes largely undetected on the traditional opiate assay, thus necessitating this more specific adjunctive screen. Many immunoassays for methadone are designed to detect the parent compound due to the fact that about one third of the drug is excreted unchanged in the urine, however many factors can make the parent compound harder to detect such as urine pH.[90] Thus, many newer generation EIAs also detect the primary metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), in order to extend the time of detection and to negate the variations in detectability due to patient-specific factors.[1,91]

Opioid Series—Buprenorphine

Buprenorphine is a semisynthetic opioid analgesic derived from thebaine, one of the natural alkaloids extracted from the opium poppy, which features extensive side chains and increased lipophilicity. It is typically used in the management of opioid dependency and detoxification on account of its partial agonist properties at the mu opioid receptor and antagonist properties at the kappa and delta opioid receptors.[92] Despite its use in treatment of opioid addiction, buprenorphine itself can also be addictive and misused.[93] The use of buprenorphine in opioid dependency programs and the addiction potential of the drug necessitate an immunoassay to test for misuse. Because of buprenorphine's semisynthetic nature, the traditional opiate immunoassay will not reliably detect its presence in urine.[18] Unfortunately, the immunoassay specific for buprenorphine also displays some cross reactivity with other commonly prescribed and abused opioid analgesics.[58,60]

Phencyclidine

Due to the fact that phencyclidine (PCP, "angel dust") is no longer widely available in the United States[1] and its use is confined to few, select urban areas,[94] a positive PCP immunoassay result is more likely to be due to cross reactivity with other drugs than actual intoxication with PCP. The phencyclidine immunoassay has significant disadvantages with regard to specificity and clinical utility. Many sources of inappropriately positive results are due to cross reactivity with nonstructurally related compounds (see Appendix A). Patients who have ingested PCP present with a fairly unique clinical picture consisting of retrograde amnesia, nystagmus, hypertension, and psychomotor stimulation[95] and should be able to be treated without aid of the urine drug immunoassay.

Marijuana

Immunoassays used to detect marijuana use are typically designed to detect 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (9-carboxy-THC), the major metabolite of marijuana found in the urine. In general, these EIAs exhibit good sensitivity and specificity for 9-carboxy-THC.[2] As expected, pure pharmaceutical grade THC (Marinol®, generic: dronabinol), Food and Drug Administration (FDA) approved for cachexia related to AIDS and prophylaxis of chemotherapy-induced nausea and vomiting, will reliably give a positive result on the immunoassay for THC.[1] Additionally, passive marijuana inhalation and/or ingesting hemp-containing foods do not typically elicit a positive urine immunoassay result for THC.[2,96,97] Unfortunately, there has been an increase in popularity of synthetic and designer cannabinoids (for example, ''spice'' and ''K2'') that are touted as being stronger and legal alternatives to traditional cannabis.[98] The immunoassays for THC are unable to detect these new synthetic compounds and more advanced methods of detection such as chromatography and/or spectrometry are required in order to elucidate the presence of these more complex designer compounds.[2]

Lysergic Acid Diethylamide

Although the use of lysergic acid diethylamide (LSD) has remained low over recent years, the use of urine drug screens for ''acid'' is still utilized today. More potent, dangerous psychedelic drugs such as the substituted phenethylamines (''bath salts'' and ''2C'' drugs) and tryptamines have become much more popular in part due to their more potent effects, but also due to their accessibility over the internet and lack of regulation under federal law.[8] Despite the adoption of these new hallucinogens by ''trip seekers,'' LSD continues to be used by a select few and knowledge of the immunoassay used to detect its presence in urine will be useful. The immunoassay for LSD is inherently susceptible to inappropriately positive results due to the fact that LSD is extensively metabolized and only a very small fraction of the parent molecule appears in urine.[99] This translates to an immunoassay with high sensitivity, but low specificity. Newer generation LSD immunoassays are designed to target the primary metabolite 2-oxo-3-hydroxy-LSD, which may improve detectability as it achieves higher and more detectable concentrations in the urine.[91]

Tricyclic Antidepressants

Today, tricyclic antidepressants (TCAs) are more often used in the settings of neuropathic pain, headache and migraine prophylaxis, fibromyalgia, insomnia, irritable bowel syndrome, and less in the setting of depressive disorders.[3] This translates to potentially less severe TCA overdoses due to less prevalence and accessibility of the higher strengths that were typically used for treating depressive disorders. Unfortunately, the 3 ring pharmacophore that gives TCAs their name is also found in the structures of other classes of therapeutic agents including some skeletal muscle relaxants, atypical antipsychotics, anticonvulsants, and antihistamines. Due to the high prevalence of inappropriate results, other assessments should be recommended if TCA toxicity is suspected. An electrocardiogram (ECG) can show many indicators of TCA toxicity (eg, an R' wave, a widened QRS complex, and a prolonged QTc interval) and can be obtained in a much shorter time period.[3] Gathering a medical and medication use history and physical assessment can also aid in diagnosing TCA toxicity and will allow the provider to treat the patient long before getting a urine sample and subsequent results from the laboratory.

Table 1. Drugs of Interest Not Detected By Routinely Used Urine Drug Immunoassays

- Non-benzodiazepine hypnotics
  - Zolpidem, eszopiclone, zaleplon
- Ketamine (“special K”)
- Mescaline (“peyote”)
- Psilocybin (“magic mushrooms”)
- Gamma-hydroxybutyrate (GHB)
- 1,4-Butanediol (precursor to GHB)
- Chloral hydrate
- Synthetic and designer cannabinoids (“spice” and “K2”)
- Tryptamines
- Phenethylamine derivatives (synthetic stimulants, “bath salts”, “2C” drugs)
- Imidazoline receptor agonists (clonidine, tetrahydrozoline, oxymetazoline)

Drugs of Interest Not Detected By Routinely Used Urine Drug Immunoassays

As important as it is to know the drugs commonly detected using routine urine drug screening via immunoassay, it is also important to know which drugs of interest may not be detected and/or tested for routinely. Table 1 provides a list of drugs of interest that may be involved in suicide attempts, accidental overdoses, unintentional ingestions, drug-assisted sexual assaults, and other situations which may warrant urine toxicology testing. Despite the development and current or eventual availability of immunoassays for these specific substances, cost, clinical utility, reliability, and frequency of use are potential prohibitive factors and may limit the use of these much more specific immunoassays within contemporary health care settings.

Strategies for Interpretation

First and foremost, knowledge of the limitations of the particular immunoassay the laboratory uses will prove to be an essential strategy for accurately interpreting results from urine drug screenings. Not all laboratories utilize the same immunoassays, detection methods, and/or threshold values. Knowing an institution's specific practices will allow clinicians to be prepared and proficient at interpreting the results of urine drug screens regardless of the specific assay type being used. The only ways to know precisely what type of immunoassay a laboratory uses is to get the appropriate package inserts from the laboratory or to simply ask clinical laboratory scientists for more information.

Not knowing the laboratory's screening capabilities and shortcomings can result in being misled by results and this can and has resulted in patient harm.

Second, the patient's unique history and clinical presentation can tell us a lot more than the urine drug immunoassays currently used in practice today. Utilizing pharmacists who conduct medication reconciliation and/or medication therapy management (MTM) services will facilitate the collection of information that will provide a much more complete clinical picture. Literature suggests that medication reconciliation completed by pharmacists is more accurate and trusted by physician colleagues.[100,101] This translates to more accurate medication lists, information regarding refill quantities and dates, and communication with the patient's source of prescription and over-the-counter (OTC) medications which will allow clinicians to more effectively assess the probability for misleading results from urine drug immunoassays. The medication use patterns and past medical history of the patient may be more predictive of the likelihood of toxicity than a urine drug screen administered at one point in time.

Finally, the window of time that drugs are detectable after the patient took their last dose of any given substance must also be considered. The time frame of a positive or negative result is especially important due to the fact that is it easy to become reliant on these results and accept them as the only possible explanation for a given clinical scenario, even though in many cases, there is another explanation. For many acute ingestions, the detectable window may be on the order of a day or two. In contrast, if a patient has used a particular substance on a chronic basis, the detection time in the urine may be much longer.[2,91] For example, a single use of marijuana may be detectable for only 3 days, but chronic use can sometimes be detected for up to 30 days after the last dose.[91] Appendix B provides a list of commonly detected drugs of abuse and their approximate detection times in urine. Additional variables can complicate the estimation of these times, including the dose of the drug taken, frequency of use, individual variations in metabolism and/or excretion, urinary pH, and drug distribution.[1]

Clinical Applications

Results as Proof

If a patient presents with tachycardia, altered mental status, and hyperthermia and subsequently tests positive for BE (the cocaine metabolite), it is possible that this represents an acute cocaine intoxication, but it may be possible the instance of cocaine use causing the positive result was up to 5 days ago and the current urgent clinical scenario is due to the result of serotonin syndrome, neuroleptic malignant syndrome, sepsis, thyroid storm, or number of other potential critical conditions. Clinicians may very easily miss these other critical diagnoses because of reliance on the results of urine drug immunoassays and interpreting the results as the cause of the current clinical scenario.

Mismanagement of Patients

If a patient presents with central nervous system (CNS) depression, miosis, and respiratory depression complicated by hypoxia and hypercarbia, the likelihood this patient was exposed to an opioid is high and this patient should receive a trial of naloxone even in the context of a negative immunoassay for opioids. The potential lifesaving and diagnostic benefits of naloxone therapy in this case outweigh the risks associated with the use of the medication. Theoretically this trial of naloxone could induce opioid withdrawal in some patients, such as chronic opioid users, if not dosed appropriately. Although uncomfortable, opioid withdrawal is not a life-threatening condition unlike the potentially severe CNS and respiratory depression secondary to opioid use. The subsequently obtained medication history of the patient may reveal that he or she is chronically on methadone for pain, which may explain the negative drug screen result. In other words, this patient may have taken one or more of the many semisynthetic or fully synthetic opioids with enough structural dissimilarity to the natural opiates (morphine and codeine) that it goes undetected on the administered urine drug screen. If a clinician was to see a negative immunoassay for opioids and neglect to give naloxone, the mismanagement of the patient may result in harm. Gathering a history (including medication history) and physical assessment prove much more valuable in guiding medical management of the patient. For this reason, it is reasonable to recommend against routinely obtaining urine drug immunoassay screens on intoxicated or suspected overdose patients as the results provided by the immunoassays may be misinterpreted or result in mismanagement of the patient's medical therapy to the point of harm.

Legal Implications

If a patient comes in and shows signs of child abuse or drug-assisted sexual assault, a clinician may believe that a urine drug immunoassay is indicated and would be helpful to determine if the victim had been drugged. Remember from above that most of the benzodiazepines and other sedative-hypnotics that would commonly be seen in this context do not reliably produce positive results on urine drug screens done with immunoassays. If the clinician isn't aware of the potential shortcomings of the EIAs, he or she may not contemplate more advanced detection methods or "confirmatory testing" and these results could mislead the health care team (and subsequently the litigation team) to conclude that there was no drug involved, even though a multitude of drugs that are not reliably detected could have been used to sedate the victim. Thus, inappropriate drug screening practices in this case could provide support for the case of the child abuser or the perpetrator of drug-assisted sexual assault and have disastrous legal implications.

Conclusion

Urine drug screens have their purpose in the continuum of care that is provided to patients, however, the limitations of the

urine drug immunoassays that are used must be realized by all clinicians, but most importantly the ordering provider and the interpreter. Recent literature suggests that there is a general lack of understanding of the shortcomings of these assays by the clinicians who are frequently ordering them, regardless of practice setting.[102,103] Clinicians must understand that the urine EIAs only provide qualitative, presumptive results and that all positive results must be confirmed via tried and proven analytical methods of detection such as GC/MS also referred to as ''confirmatory testing.'' These presumptive results should also not preclude the clinical judgment of the clinician based on vital signs, physical examination, medication use patterns, past medical history, and other more definitive diagnostic tests such as an ECG. Although rapid urine drug screening has become the standard of care in many situations, such as major trauma or suicidal ideation, keep in mind the numerous limitations of these screenings and that this standard of care may be dictated more by classic dogma than the actual clinical utility of the immunoassay itself. Although an initial screening using urine immunoassays is a fast and relatively inexpensive method to determine the presence of a drug or drug class, the EIAs suffer from cross reactivity to structurally related and in some cases, structurally unrelated compounds. Inappropriately positive and negative results from these tests are all too common. Clinical decision making should be guided not by urine drug screening, but by good assessment of all aspects of the patient history, objective presentation, and acknowledgment of the shortcomings of the detection methods. The proper utilization of clinical resources, including toxicology services, clinical pharmacists, and poison information centers should result in the realization that urine drug immunoassays may not improve outcomes in acute patient management. The use of urine drug screening in less acute situations and legal settings also needs to be evaluated with the same set of clinical resources in order to reach accurate conclusions to assure that the resulting actions that are taken by the clinician or by the law are warranted.

Appendix A

Commonly Used Urine Immunoassays and Reported Sources of Inappropriate Results

Immunoassay (with common targets)	Reported Sources of Inappropriate Results	
	Positive	Negative
Amphetamines Common targets D-amphetamine D-methamphetamine	Amantidine[22], atomoxetine[23], bupropion[24,25], chloroquine[26], ephedrine[27], pseudoephedrine[27], phenylephrine[27], metformin[28], phentermine[29], ranitidine[30], selegiline[31], labetalol[32], some phenothiazines (chlorpromazine[33], promethazine[33]), trazodone[34,35], and some tricyclic antidepressants (doxepin[22,36], desipramine[22,36])	MDA[5], MDMA ("ecstasy" or "molly") and its derivatives[5], substituted phenethylamine derivatives[5,9,37] ("bath salts" and "2C" drugs)
Barbiturates Common targets Secobarbital	NSAIDs such as ibuprofen[38] or naproxen[38]	Sodium thiopental[12]
Benzodiazepines Common targets Nordiazepam (met) Oxazepam (met)	Sertraline[1,39], oxaprozin[40-42], efavirenz[43]	Clonazepam[1,6,18], lorazepam[1,6,18], alprazolam[18], flunitrazepam[18], midazolam[18,44], chlordiazepoxide[45,46]
Cocaine Common targets Cocaine Benzoylecgonine (met)	Coca tea[17,65], some forms of yerba mate ("mate de coca")	Fluconazole has been implicated in causing inappropriately negative results on the cocaine urine drug screen, however current evidence points to the fact that it actually interferes with confirmatory testing via GC/MS rather than the immunoassay[6]
Opiates Common targets Morphine Codeine	Poppy seed containing foods[1,2,18,48], some fluoroquinolone antibiotics (levofloxacin[49], ofloxacin[49]), imipramine[46], naltrexone[46], naloxone[50], rifampin/rifampicin[51]	Hydrocodone[2,18],hydromorphone[2,18], oxycodone[2,18], oxymorphone[2,18], fentanyl[2,18], methadone[1,2,18], tramadol[18,47], buprenorphine[2,47], meperidine[18,47]
Oxycodone Common targets Oxycodone Oxymorphone (met)	None known—oxycodone-specific immunoassays have exceptional specificity and therefore exhibit almost no cross reactivity	None known—oxycodone-specific immunoassays have adequate sensitivity to detect oxycodone and/or oxymorphone in urine

(continued)

Appendix A (continued)

Immunoassay (with common targets)	Reported Sources of Inappropriate Results	
	Positive	Negative
Methadone Common targets Methadone EDDP (met)	Doxylamine[52], diphenhydramine[53], verapamil[54], verapamil metabolites[54], quetiapine[55,56], tapentadol[57]	None known—methadone-specific immunoassays have adequate sensitivity to detect methadone and/or EDDP in urine
Buprenorphine Common targets Buprenorphine Norbuprenorphine (met)	Morphine[58,59], morphine-3-glucuronide[59] (metabolite), codeine[59], methadone[59], tramadol[60]	None known—buprenorphine-specific immunoassays have adequate sensitivity to detect buprenorphine in urine
Phencyclidine (PCP) Common targets Phencyclidine	Venlafaxine[61,62], O-desmethylvenlafaxine[61,62] (metabolite), dextromethorphan[63], ibuprofen[63], thioridazine[64], diphenhydramine[64], tramadol[65,66], ketamine[67], MDPV[68] ("bath salt"), lamotrigine[69], zolpidem[70]	None known—phencyclidine-specific immunoassays have adequate sensitivity to detect phencyclidine in urine
Marijuana (THC) Common targets 9-Carboxy-THC (met)	Efavirenz[71], promethazine[45], some NSAIDs (ibuprofen[72], naproxen[72]), pantoprazole[1,73]	Synthetic and designer cannabinoids ("spice", "K2")[2,74]
Lysergic acid diethylamide (LSD) Common targets LSD 2-Oxo-3-hydroxy-LSD (met)	Fluoxetine[8], buspirone[8], haloperidol[8], labetalol[8], risperidone[8], trazodone[8], doxepin[8], diltiazem[8], verapamil[8], amitriptyline[8], metoclopramide[8], methylphenidate[75], imipramine[75], ergonovine[75], fentanyl[75], norfentanyl[75] (metabolite), sertraline[75], bupropion[76], prochlorperazine[77]	None known—LSD-specific immunoassays have adequate sensitivity to detect LSD and/or 2-oxo-3-hydroxy LSD in urine
Tricyclic antidpressants (TCAs) Common targets Amitriptyline Imipramine	Cyclobenzaprine[78], quetiapine[79-81], carbamazepine[82-84], cyproheptadine[85], hydroxyzine[86], cetirizine[86], diphenhydramine[87]	None known—tricyclic antidepressant-specific immunoassays have adequate sensitivity to detect TCAs in urine

Abbreviations: met, metabolite; NSAIDs, nonsteroidal anti-inflammatory drugs; MDPV, methylenedioxypyrovalerone; MDMA, 3,4-methylenedioxy-methamphetamine; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; GC/MS, gas chromatography/mass spectrometry; 9-carboxy-THC, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol.

Appendix B

Estimated Detection Times in Urine of Commonly Used Drugs of Abuse[a]

Drug Class and Specific Compound	Detection Window From Last Use
Amphetamines	
• D-amphetamine	3 days
• D-methamphetamine	3 days
• MDMA (ecstasy or molly)	2 days
• Methylphenidate	1-2 days
• Pseudoephedrine/ephedrine	5 days
Barbiturates	
• Phenobarbital (long acting)	15 days
• Butalbital (intermediate acting)	7 days
• Pentobarbital (short acting)	3 days
• Secobarbital (short acting)	3 days
Benzodiazepines	
• Diazepam and/or nordiazepam (metabolite)	10 days
• Alprazolam	5 days
• Lorazepam	5 days

(continued)

Appendix B (continued)

Drug Class and Specific Compound	Detection Window From Last Use
• Temazepam	5 days
• Clonazepam	5 days
• Chlordiazepoxide	5 days
• Flunitrazepam	5 days
• Midazolam	2 days
Buprenorphine	
• Buprenorphine and/or norbuprenorphine (metabolite)	7 days
Cocaine	
• Cocaine	< 1 day
• Benzoylecgonine (metabolite)	5 days
LSD	
• Lysergic diethylamide (LSD)	< 1 day
• 2-Oxo-3-hydroxy-LSD (metabolite)	5 days
Marijuana	
• Single use/very occasional use (1-2 times per week)	3 days
• Moderate use (4-6 times per week)	5 days
• Heavy use (daily use)	10 days
• Chronic heavy use	30 days
Opiates	
• Morphine	3 days
• Codeine	3 days
Semisynthetic opioids	
• Hydrocodone	3 days
• Hydromorphone	3 days
• Oxycodone	3 days
• Oxymorphone	3 days
Fully synthetic opioids	
• Fentanyl and/or norfentanyl (metabolite)	3 days
• Methadone and/or EDDP (metabolite)	1-7 days
Phencyclidine	
• Phencyclidine (PCP)	8 days

Abbreviations: MDMA, 3,4-methylenedioxy-methamphetamine; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.
[a] Data from Reference 91.

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