

Urine drug screens: Considerations for the psychiatric pharmacist

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Abstract

Introduction: Proper psychiatric evaluation of patients necessitates that the clinician be vigilant in ruling out secondary causes of symptoms, such as substance-induced symptoms. Immunoassay-type urine drug screens (UDSs) offer clinicians rapid drug screen results, ease of use, and inexpensive cost. Unfortunately, these screens are not without their limitations. This review aims to outline the nuances and limitations of immunoassay UDSs and to provide the clinician with information that facilitates more accurate interpretation of UDS results. Specifically, false positive results associated with psychiatric medications and the availability and methods for acquisition of commercialized UDS masking agents will be reviewed.

Methods: A literature review was conducted to identify false positive UDSs associated with psychiatric medications. References for each article identified were also reviewed. Additionally, a Google® search was conducted to identify commercially available preparations used to mask UDS results and the methods of acquisition of these products.

Results: A total of 14 articles were identified using PubMed. No articles for mood stabilizing agents were identified. Entering the phrase *how to pass a drug test* into Google® search yielded about 12.6 million results, and select references were reviewed based on relevance and user reviews.

Discussion: Several psychiatric medications are documented as potential sources of false positive UDSs. Additionally, several agents are available for consumer purchase that may result in false negative UDSs. The clinician must be vigilant in interpreting immunoassay UDS results and should utilize more advanced forms of testing as clinically appropriate.

Keywords: urine drug screens, false positive results, masking agents

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employed by kits available for over-the-counter (OTC) consumer purchase.¹ Multiple psychiatric medications are documented in the literature to produce erroneous immunoassay UDS results. A comprehensive review of false positive UDS results associated with commonly prescribed medications was published in 2010, and of the 20 medications reported as sources of false positive UDSs, 9 fell into psychiatric medication classes.² Similarly, many of the most commonly abused drugs in the United States, including cannabis (tetrahydrocannabinol), methamphetamine, cocaine, and opioid analgesics, have known idiosyncrasies with respect to immunoassay-type UDSs.³ Immunoassay-type UDSs are among the most popular tools utilized for drug screening in social, professional,

Introduction

The immunoassay urine drug screen (UDS) is the principle method of drug testing utilized for initial screening at the point of direct patient care, and it is also the method



athletic, and medical environments despite several alternative screening options and problematic limitations.¹ Many substances are eliminated through and detectable for an extended period of time in the urine.⁴ However, several factors can contribute to inaccurate UDS results, including persistence of substance use, amount of substance used, use of certain prescription and OTC medications, use of some dietary supplements and masking agents, and the pharmacokinetic profile of the individual substance and its metabolites.¹ The quality of the urine sample itself (ie, urine creatinine, temperature, and pH) may also adversely affect UDS results, should one or all of these parameters fall outside of the normal range.³

The numerous confounders that may affect UDS results allow for complex, unclear clinical presentations to arise. In some instances, patients may present with clinical manifestations of withdrawal or substance-induced psychiatric disturbance while simultaneously producing a false negative UDS. Conversely, patients may present without clinical signs or symptoms of illicit substance use and deny use of any illegal substances while producing positive UDS results (eg, false positive results as a consequence of certain prescription medications).

Immunoassay UDS

Immunoassay UDSs produce a qualitative assessment of a sample that is determined by drug-specific antibody reactivity at a predetermined cutoff concentration.⁵ Several types of immunoassays exist and vary in the number and threshold concentration of substances detected.⁵ Standard 5-panel tests typically screen for amphetamines, cocaine and metabolites, opiates, marijuana and metabolites, and phencyclidine. This group of substances is in alignment with the Substance Abuse and Mental Health Services Administration (SAMHSA) mandatory guidelines for federal workplace testing. SAMHSA has defined the various predetermined cutoff concentrations for these 5 substances.⁶

Immunoassay analysis can be conducted in a variety of ways, including enzyme-multiplied immunoassay technique, radioimmunoassay, fluorescence polarization immunoassay, and particle immunoassay, with enzyme and particle-type immunoassays being the most utilized in hospital laboratories.^{1,5} Rapid results, ease of use, and inexpensive cost make immunoassay UDSs an attractive first-line screening option.¹ However, several limitations of this testing technique have been documented in the literature. Primarily, all immunoassay UDSs possess the potential to produce false positive results.² Thus, these tests are incapable of providing validated results on their own. Rather, immunoassay results must be considered tentative until validated by a more labor-intensive and

costly laboratory-based test, such as gas chromatography–mass spectrometry (GC-MS).¹ Second, the qualitative nature of these screens leaves the clinician without any insight into the route of administration of the substance detected, the duration of use, or the amount of substance used.⁵

Methods

A number of medications, OTC products, and dietary supplements have been implicated in causing false positive UDS results. The scope of this review will be focused specifically on psychotropic medications and certain agents of abuse. A literature review was conducted for psychiatric classes of medications, including antipsychotics, antidepressants, mood-stabilizing agents, and certain agents of abuse, including opioids, amphetamines, marijuana, phencyclidine, and cocaine. English-language articles were reviewed and located utilizing PubMed and the medical subject heading terms *false positive reaction* and *antipsychotic agents* or *antidepressant agents* or *antimanic agents*. References for each article identified were also reviewed. Additionally, the Google® search engine was used to search the phrase *how to pass a drug test*. This search was used to identify commercially available preparations used to mask UDS results and the methods of acquisition of these products.

Results

A total of 14 articles were identified using PubMed, 10 for antidepressants and 4 for antipsychotics. No articles for mood-stabilizing agents were identified even when using individual medication names, including *divalproex*, *carbamazepine*, *oxcarbazepine*, *lithium*, *lamotrigine*, and *gabapentin*. Additionally, no results for false positive cocaine/cocaine metabolite results associated with psychotropic use were found. The full list of psychotropic medications associated with false positive results can be found in the Table. The Google® search yielded about 12.6 million results, and select references were evaluated and included based on relevance and user reviews.

False Positives Associated With Psychotropics Listed by Agent of Abuse

Opiates/Opioids

Opiates are readily detected by UDS. However, the low specificity and qualitative nature of immunoassay UDSs does not allow for identification of the specific agent used without more advanced testing. For example, individuals using codeine may test positive for diacetylmorphine and morphine.^{3,7,8} Similarly, hydrocodone can result in a false positive hydromorphone screening given that hydrocodone is postulated to be metabolized to hydromorphone

TABLE: Psychiatric medications documented as causing false-positive results on urine drug screens

False Positive	Psychiatric Medication	Study	n, % ^a	Immunoassay
Methadone	Chlorpromazine ⁹	Observational (n = 45)	1.5	Kinetics Interaction of Microparticles in Solution
	Thioridazine ⁹		0.3	
	Clomipramine ⁹		0.3	
	Quetiapine ¹⁰	Case report	...	COBAS Integra Methadone II test kit
	Quetiapine ¹¹	Case series (n = 10)	...	COBAS Integra Methadone II test kit
	Quetiapine ¹²	Retrospective chart review ^b (n = 12)	...	Methadone II
Amphetamines	Promethazine ¹³	Observational (n = 22)	36	EMIT® II Monoclonal ^c
	Promethazine ¹⁴	Observational (n = 23)	13	EMIT® II Monoclonal ^c
	Chlorpromazine ¹⁴	Observational (n = 18)	66	
	Bupropion ¹⁵	Case report	...	EMIT® U AMP
	Bupropion ¹⁶	Case report	...	EMIT® II Monoclonal ^c
	Bupropion ¹⁷	Retrospective chart review (n = 362)	14.6	Syva EMIT® II Plus
	Bupropion ¹⁸	Case report	...	Cloned Enzyme Donor Immunoassay
	Trazodone ¹⁹	Case report	...	EMIT® I
	Trazodone ²⁰	Case report	...	Triage® Drugs of Abuse Panel Plus Tricyclic Antidepressants
Phencyclidine	Selegiline ²¹	Case report	...	Methamphetamine RIA screening test
	Thioridazine ²⁵	Case report	...	EMIT® II
	Mesoridazine ²⁵			
	Venlafaxine ²⁶	Case report	...	INSTANT-VIEW Multi-Drug Screen Urine Test
	Venlafaxine ²⁷	Case series (n = 3)	...	Syva® RapidTest d.a.u. ^{®9} Test Panel
	Venlafaxine ²⁸	Case report	...	Abbott AxSYM

^an, % reported only when less than 100% of subjects had false positive results from psychotropics.

^bStudy reviewed only false positive patient cases.

^cEMIT® II Plus Monoclonal Amphetamine/Methamphetamine

through an unknown metabolic pathway.⁷ Timing of the UDS sample can also affect detection of certain opiates. For instance, the metabolite 6-monoacetylmorphine can confirm use of heroin, but the window for metabolite detection is only a few hours after last use (less than 12 hours).^{7,8} Aside from the mentioned limitations with UDS detection of opioids and opiates, certain psychotropic agents may also interfere with UDS results by producing false positive results.

Chlorpromazine and thioridazine have been cited in the literature as potential sources of false positive UDS results for methadone. In 1 study, drug-free urine samples were supplemented with a variety of psychotropics and then tested using the Kinetics Interaction of Microparticles in Solution (KIMS, Roche) monoclonal antibody assay, GC-MS, and a methadone metabolite assay. Chlorpromazine at concentrations of 20 mg/L and thioridazine at concentrations of 100 mg/L resulted in false positive results for methadone.⁹ Olanzapine, risperidone, and clozapine were tested at concentrations of up to 100

mg/L, and none were associated with cross-reactivity.⁹ Nevertheless, the second-generation antipsychotic, quetiapine, has been documented in case reports and retrospective chart reviews to result in false positive methadone results on UDS, both in adolescent and adult patients.¹⁰⁻¹²

In one publication previously mentioned, several antidepressants were also evaluated using the KIMS (Roche) monoclonal antibody assay, GC-MS, and a methadone metabolite assay.⁹ Clomipramine at concentrations of 100 mg/L was associated with cross-reactivity for methadone. Sertraline, paroxetine, citalopram, and venlafaxine were tested at concentrations up to 100 mg/L, and none were found to have appreciable cross-reactivity.⁹

Amphetamines

Among the articles identified by our literature review, false positive amphetamine results associated with psychotropic use occurred more frequently than any other false positive result. This is consistent with other reviews of false positive UDS results.² Agents from both antipsychotic and antide-

pressant medication classes have been implicated in causing false positive UDS findings for amphetamines.

Phenothiazine antipsychotics (ie, promethazine and chlorpromazine) are described in the literature as causes of false positive amphetamine results.^{13,14} Inclusion criteria for one 11-month emergency department study required patients to have detectable serum concentrations of promethazine and an immunoassay UDS performed during the course of the admission (n = 22). Within this sample, 8 (36%) patients had false positive amphetamine results.¹³ Similarly, promethazine and chlorpromazine were shown to cause false positive amphetamine results using the same immunoassay (EMIT® II amphetamine/methamphetamine assay) in an earlier publication.¹⁴ In this study, 135 urine samples from 104 subjects were collected over an 8-week period. All urine samples evaluated with the polyclonal EMIT® d.a.u.TM assay and GC-MS were negative. Samples tested with the EMIT® II immunoassay produced false positive amphetamine results in 12 of 18 subjects prescribed chlorpromazine. Chlorpromazine doses greater than 100 mg daily were most frequently associated with positive screenings (n = 6). One subject taking chlorpromazine 25 mg daily produced false positive amphetamine results. Promethazine was prescribed to 23 subjects and produced false positive amphetamine results in 3 subjects. Promethazine doses of 50 mg or greater were used by all 3 subjects.¹⁴

Multiple antidepressants are cited in the literature as the source of false positive amphetamine results. Several case reports have documented bupropion as the source of false positive UDS results for amphetamine.^{15,16} A retrospective review of all emergency department patients who underwent UDS between January 1, 2006, and July 31, 2007, was conducted in response to these reports. Syva EMIT® II Plus immunoassay reagents were used on all samples, and positive results were confirmed by GC. Urine samples were positive for amphetamine in 362 (3.6%) cases and confirmed by GC in 234 of these cases. Among the confirmed cases, bupropion was documented as used by 3 (1.3%) patients. Among the 128 (35%) unconfirmed cases, prescription use of bupropion was reported in 53 (41%) patients.¹⁷ A case report for bupropion interfering with the Cloned Enzyme Donor Immunoassay exists, in which a 50-year-old subject was found to have positive UDS results for amphetamines and LSD. GC-MS and liquid chromatography–mass spectrometry identified bupropion as the interfering agent. The presence of amphetamines and LSD could not be confirmed.¹⁸ Among other antidepressant classes, 2 case reports for false positive amphetamine results associated with trazodone have been published, one of which involved trazodone overdose.^{19,20} Older classes of antidepressants have also been implicated as a source of false positive UDS results. The

monoamine oxidase inhibitor selegiline, which is metabolized to l-amphetamine and l-methamphetamine, has been documented to cause false positive results for amphetamine.²¹

Outside of psychiatric medication classes, other products containing dimethylamylamine (DMAA), a straight chain amine with a similar structure to amphetamines, have notably become a costly issue leading to a high number of confirmatory tests needed.²² Usually, a GC-MS test is necessary to confirm the absence or presence of this substance in UDSs. DMAA was first found in nasal decongestants as a vasoconstrictor in the nasal mucosa. Today, it is available in nutritional and bodybuilding energy supplements.²² More frequently encountered problematic agents are OTC cold and cough medications containing ephedrine, phenylephrine, and pseudoephedrine, which have the ability to cross-react with immunoassays.²² There is also potential for cross-reactivity with substances that have a similar structure to amphetamines. Phenylephrine, an alpha-1 adrenergic agonist, may yield false positive results due to cross-reactivity.²³

Marijuana and Metabolites

Our literature search did not yield any publications regarding antipsychotic- or antidepressant-associated false positive results for marijuana. When performing a UDS, most drugs and their metabolites are detectable within 1 to 3 days of last use.³ Marijuana is a notable exception because, given the substance's high lipophilicity, it can be detected in the urine anywhere from a week to over a month since last use, depending on the subject's chronicity and quantity of use.⁷ Theoretically, synthetic cannabinoids, such as dronabinol and nabilone, and the natural pharmaceutical product nabiximols could yield positive UDS results for marijuana metabolites. However, only dronabinol and nabiximols have been documented to produce positive immunoassay results and a positive confirmatory assay for the metabolite 11-nor-9-carboxy-D₉-tetrahydrocannabinol.⁷ There is question as to whether passive exposure to marijuana smoke would generate positive UDS results. Although not impossible, results have shown that positive results from passive exposure to marijuana smoke are extremely unlikely and that the exposure would have to be significant and recent to elicit a positive UDS. Even studies demonstrating real-world scenarios have failed to prove that passive (or second-hand) marijuana smoke exposure will yield a positive finding on UDS.^{1,7,24}

Phencyclidine

Phencyclidine is among one of the standard 5-panel tests outlined by SAMHSA.⁶ Our literature search yielded 4 articles documenting psychotropic-associated false positive phencyclidine results, 1 for antipsychotics and 3 for antidepressants, respectively.

Thioridazine is documented in 1 case report as the cause of a positive phencyclidine UDS result using the EMIT® II assay.²⁵ The presence of phencyclidine was not confirmed when tested using GC-MS. The authors concluded that the combined presence of thioridazine and mesoridazine were sufficient in producing false positive results for phencyclidine.²⁵

The serotonin and norepinephrine reuptake inhibitor venlafaxine and its metabolite, O-desmethylvenlafaxine, have been documented to cause false positive results for phencyclidine in multiple case reports.²⁶⁻²⁸ One publication reported 3 cases of false positive phencyclidine results associated with venlafaxine, all of which were not confirmed when samples were tested by GC-MS.²⁷ False positive results associated with venlafaxine are theorized to be secondary to cross-reactivity with the phencyclidine antibody when combinations of the metabolite and active compound are both present.²⁷

Commercially Available Masking Agents and Methods for Acquisition

Both commercially available products and various household items have been documented to interfere with detection of substances through immunoassay UDS. UDS masking has become an increasingly lucrative business, given that many US employers require, at least minimally, a UDS upon hire. The efficacy of UDS tampering is affected by multiple elements, including time since last use, amount of substance used, drug and adulterant levels in urine, specific test used, fluid intake, and several other factors.²⁹

A review by Jaffee and colleagues outlines several commercially available and OTC tampering products and notes that the majority of commercial masking agents contain either glutaraldehyde, nitrite, pyridinium chlorochromate, or peroxidase and peroxide.²⁹ Some tampering agents are aimed at urine sample dilution and acidification. These products generally contain combinations of caffeine, vitamins, and cranberry and advise the consumer to drink as much as 1 gallon of water with administration.²⁹ Urine dilution and orally administered masking agents are sometimes detectable in more sophisticated forms of drug testing or on visual inspection.²⁹ For this reason, manufacturers may supply consumers with synthetic urine, such as Quick Fix®, or agents formulated to be added directly to a urine sample, such as Urine Luck™.

Retailers, often referred to as *head shops* or *smoke shops*, are cited as vendors of UDS detoxifying products. Certain websites detail instructions for the purchase of masking agents within local shops.³⁰ When an individual is interested in the purchase of a masking agent within a store, he or she is instructed to ask for the merchant's most

potent *detoxifier* and to specifically avoid phrasing such as *drug test* or *preemployment* in order to avoid disengagement of the sales clerk and failure to complete the sale. Interested buyers are encouraged to do their homework prior to purchase of one of these products as each product is touted to be better suited for certain recreational agents of abuse. Aside from in-store purchase, several products, such as Clean-X®, Absolute Detox®, and a wide variety of *detoxifying teas*, can readily be found on the Internet and ordered with a credit card for home delivery. Prices for these products can range anywhere from US\$10 for oral capsules enhanced with cranberry, such as Nature's Secret Urinary Cleanse and Flush™, to US\$45 for a 16-ounce detoxifying drink, such as Rely Detox®.

Conclusion

UDSs are useful tools at the point of direct patient care and are widely used in multiple settings. The clinician must be cognizant of their limitations and pitfalls in order to utilize UDSs appropriately. Several psychiatric medications are documented as potential sources of false positive UDSs. Additionally, several OTC agents are readily available for consumer purchase and can result in false negative UDSs. False positive UDS results can have significant negative impacts on patient outcomes, including dismissal from drug treatment programs, incarceration, child-custody difficulties, and loss of social support. Positively identifying illicit substance use is equally important as this can further explain patient presentation and preclude certain psychiatric diagnoses.³¹ The clinician must be vigilant in interpreting immunoassay UDS results and should utilize more advanced forms of testing, particularly if potential negative social and/or legal consequences exist for the patient. Individuals should become familiar with their institution's specific tests and the sources of potential false negative and false positive results. The psychiatric pharmacist is in a unique position to monitor and critically evaluate the results of immunoassay UDSs and to serve as a resource for educating interprofessional colleagues on potential false positive results associated with psychotropic medications.

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