

# Commonly prescribed medications and potential false-positive urine drug screens

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The potential for false-positive urine drug screen (UDS) results for substances of abuse presents a therapeutic selection dilemma for the treating health care professional. While this problem is reported with specific medications, the extent of the problem in a clinic serving indigent patients and the medically underserved has not been evaluated. In particular, the use of medications with the potential for false-positive UDS results may present a significant liability for individuals required to undergo random or periodic UDSs as a component of a recovery or court-ordered monitoring program<sup>1,2</sup> or as a condition of employment.<sup>1,3,4</sup> In addition, false-positive UDS results may affect the clinician–patient relationship by raising issues of trust.<sup>5</sup> This article identifies commonly used medications associated with reports of false-positive UDSs.

## Literature review

A comprehensive literature review

**Purpose.** The implications of potential false-positive urine drug screen (UDS) results for patients receiving commonly prescribed medications were evaluated.

**Summary.** A comprehensive literature review was conducted to identify false-positive UDSs associated with all clinic formulary medications, as well as common nonprescription medications. The references of each report describing a medication whose use was associated with false-positive UDS results were also reviewed. If a class effect was suspected, additional agents in the category were searched. A total of 25 reports of false-positive UDS results were identified. Categories of medications included antihistamines, antidepressants, antibiotics, analgesics, antipsychotics, and nonprescription agents. Reports of false-positive results were found for the following formulary and nonprescription medications: brompheniramine, bupropion, chlorpromazine, clomipramine, dextromethorphan, diphenhydramine, doxylamine, ibuprofen, naproxen, promethazine, quetiapine, quinolones (ofloxacin and gatifloxacin), ranitidine, sertraline, thioridazine, trazodone, venlafaxine,

verapamil, and a nonprescription nasal inhaler. False-positive results for amphetamine and methamphetamine were the most commonly reported. False-positive results for methadone, opioids, phencyclidine, barbiturates, cannabinoids, and benzodiazepines were also reported in patients taking commonly used medications. The most commonly used tests to screen urine for drugs of abuse are immunoassays, even though false-positive results for drugs of abuse have been reported with a number of these rapid-screening products. Results from such tests should be confirmed using additional analytical methods, including gas chromatography–mass spectrometry.

**Conclusion.** A number of routinely prescribed medications have been associated with triggering false-positive UDS results. Verification of the test results with a different screening test or additional analytical tests should be performed to avoid adverse consequences for the patients.

**Index terms:** Drug abuse; Drugs, over the counter; Drugs; False positive reactions; Tests, laboratory; Urine levels

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was conducted for all medications on the formulary of Bedlam Clinic, a free evening clinic for the medically indigent or working poor, offered by the University of Oklahoma School of Community Medicine in Tulsa. The English-language literature was reviewed, utilizing databases for Ovid MEDLINE, International Pharmaceutical Abstracts, the Excerpta Medica Database, the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, and NHS Economic Evaluation Database. The search strategy was developed by a medical librarian combining the terms *false positive results*, *urine*, and *substance abuse testing* and the generic names of 116 medications. When possible, MeSH terms were used and expanded upon. Truncation was employed for a maximum number of results. In addition, the references for each medication with a reported false-positive UDS were reviewed.

Reports of false-positive UDS results were found for 25 (21.5%) of 116 formulary medications. The potential for false-positive UDS results was identified for the following medication classes on the clinic formulary: antihistamines, antidepressants, antibiotics, analgesics, antipsychotics, and nonprescription agents. Specific immunologic reagent tests have been identified with these reactions, and, in some cases, the

concentrations needed to elicit the reaction were provided.

Examples of specific medications with false-positive reports are listed in Table 1 and included brompheniramine,<sup>6,7</sup> bupropion,<sup>8,9</sup> chlorpromazine,<sup>10,11</sup> clomipramine,<sup>10</sup> dextromethorphan,<sup>12-14</sup> diphenhydramine,<sup>11,15</sup> doxylamine,<sup>16</sup> ibuprofen,<sup>14</sup> naproxen,<sup>4</sup> promethazine,<sup>17</sup> quetiapine,<sup>5,18,19</sup> quinolones<sup>1,3</sup> (ofloxacin<sup>20</sup> and gatifloxacin<sup>21</sup>), ranitidine,<sup>22,23</sup> sertraline,<sup>24,25</sup> thioridazine,<sup>10</sup> trazodone,<sup>26</sup> venlafaxine,<sup>27-29</sup> verapamil,<sup>2</sup> and a nonprescription nasal inhaler.<sup>30</sup>

Amphetamine or methamphetamine was the most commonly reported false-positive UDS result. Given the structural similarity between agents, such as ephedrine and amphetamine, this finding was not unexpected,<sup>31,32</sup> and such cross-reactivity has been previously reported.<sup>17,30,33</sup> However, cross-reactivity was reported with a structurally dissimilar agent: ranitidine. Ranitidine use resulted in false-positive results for amphetamine and methamphetamine using monoclonal antibody technology, EMIT d.a.u.

Table 1.  
**Reports of False-Positive Results of Urine Drug Screens for Selected Formulary Agents<sup>6-30</sup>**

Medication	False-Positive Result						
	Amphetamine or Methamphetamine	Phencyclidine	Methadone	Opiates	Benzodiazepines	Cannabinoids	Barbiturates
<b>Antihistamines/decongestants</b>							
Brompheniramine	X						
Diphenhydramine			X				
Doxylamine			X				
Phenylpropanolamine	X						
Nonprescription nasal inhaler	X						
<b>Antidepressants</b>							
Bupropion	X						
Clomipramine			X				
Sertraline					X		
Trazodone	X						
Venlafaxine		X					
<b>Antibiotics</b>							
Quinolones (selected agents)				X			
<b>Analgesics</b>							
Ibuprofen		X				X	X
Naproxen						X	X
<b>Antipsychotics</b>							
Chlorpromazine	X		X				
Promethazine	X						
Quetiapine			X				
Thioridazine			X				
<b>Other agents</b>							
Dextromethorphan		X					
Ranitidine	X						
Verapamil			X				

(Syva Company, Palo Alto, CA).<sup>22,23</sup> Ranitidine is available without a prescription (75 and 150 mg) and with a prescription (150 and 300 mg). In a review by the assay manufacturer, the most commonly reported dosage range associated with false-positive reports was 150–300 mg daily.<sup>23</sup> The manufacturer obtained multiple urine samples from eight subjects, five of whom had at least one false-positive result within nine hours of the last dose. The same dosage range (150–300 mg daily) was used in another study ( $n = 23$ ) to determine the urine concentration associated with a false-positive result and the time frame for this interaction after drug administration. The study revealed that urine concentrations exceeding 91 mg/L were needed to elicit a false-positive result (subject urine concentration range, 7–271 mg/L) within a short time frame after drug administration (i.e., first two voids). Of the 63 urine samples analyzed, 12 revealed false-positive results, and the urine concentration of one sample was 91 mg/L. False-positive results were not reported with polyclonal EMIT d.a.u. or TDx (Abbott Laboratories) amphetamine/methamphetamine II assays.<sup>23</sup>

False-positive reports for other nonprescription products were reviewed. Information on the prevalence of nonprescription medication use in the working poor was not found. Cold and cough medications accounted for 8.5% of the nonprescription products used by other populations, such as residents in assisted living facilities.<sup>34</sup> Common ingredients in nonprescription products may cross-react with products in commercially available methamphetamine test kits. Huang et al.<sup>6</sup> performed a systematic determination of the effect on various nonprescription product ingredients using eight methamphetamine test kits (AbuSign, accuPINCH, AccuSign, I.D. Block, Medi-Mate, QuikPac, SureStep, and Visualine) on compo-

nents (e.g., brompheniramine, chlorpheniramine, ephedrine, guaifenesin, phenylephrine, pheniramine) commonly found in nonprescription cold products. As previously reported, products structurally related to amphetamines interfered with the assay reagents and yielded false-positive results. Brompheniramine produced a positive result for amphetamine with I.D. Block at a concentration of  $\geq 1$  mg/L. In a separate case report, the use of phenylpropanolamine and brompheniramine caused a false-positive result for amphetamine with EMIT monoclonal and polyclonal products.<sup>7</sup> Confirmatory results with gas chromatography (GC) and thin liquid chromatography were negative.<sup>7</sup> Since the concentrations of phenylpropanolamine were not adequate to interfere with the test and no previous reports of false-positive results secondary to  $\beta$ -blocker use were found, the investigators theorized that the metabolites of brompheniramine might have interfered with assay results, producing a false-positive result.

Dextromethorphan is frequently included in nonprescription products as a cough suppressant. It is a congener of levorphanol, a narcotic analgesic,<sup>14</sup> yet reports of its effect on false-positive opioid results were not found. False-positive phencyclidine results were possible, however. In a case report of psychosis secondary to a dextromethorphan overdose, no immunoassay product was identified.<sup>13</sup> The authors recommended GC and mass spectrometry (GC-MS) to differentiate between phencyclidine and dextromethorphan. Marchei and colleagues<sup>14</sup> reported a false-positive phencyclidine result with the Instant-View multitest (Alfa Scientific Designs, Poway, CA) in a pediatric patient. The dextromethorphan concentration of 5000  $\mu\text{g/L}$  yielded a positive result. The patient's urine dextromethorphan concentration was 5100  $\mu\text{g/L}$ . The same investigators reported a

case of a false-positive test result for phencyclidine with ibuprofen.<sup>14</sup> One pediatric patient's urine specimen taken after ibuprofen ingestion yielded a false-positive result for phencyclidine using the Instant-View multitest. The test solution concentration needed for detection was  $4 \times 10^6$   $\mu\text{g/L}$ . Although the patient's urine concentration was lower than that of the test solution ( $3.3 \times 10^4$   $\mu\text{g/L}$ ), two factors were considered as contributors to the false-positive result: (1) the two major metabolites of ibuprofen and (2) the amount ingested. The authors theorized that cross-reactivity with the antiphencyclidine antibodies caused the false-positive test result.

Rollins and colleagues<sup>4</sup> sought to determine if episodic or chronic use of ibuprofen, naproxen, or fenoprofen could cause false-positive results. Urine samples from consenting volunteers ( $n = 120$ ) were tested with Abuscreen, EMIT d.a.u., and TDx for cannabinoids, barbiturates, and benzodiazepines. Although the investigators reported that the risk for false-positive results was low with acute or chronic ibuprofen use and chronic naproxen use, false-positive results for cannabinoids and barbiturates were reported. Naproxen, at therapeutic doses, produced one false-positive result for cannabinoids and barbiturates. Chronic ibuprofen use was associated with one false-positive result for cannabinoids and barbiturates and acute use with one false-positive result for cannabinoids. The investigators were unable to correlate the false-positive results with urine drug concentration levels, since higher levels were previously documented for these subjects and the immunoassays had not produced false-positive results for those samples. Of the immunoassays used, only the enzyme-mediated immunoassay (e.g., EMIT d.a.u.) was associated with false-positive cannabinoid results, and the fluorescence polarization immunoassay technology, used by TDx, was associated with false-

positive barbiturate results. No false-positive benzodiazepine results were reported. Metabolites for ibuprofen and naproxen were not believed to compete for cannabinoid binding sites. The investigators theorized that enzyme-reaction interference, errors in absorbance reading, or the presence of an endogenous substance may have contributed to the results. Overall, they opined that ibuprofen use (acute or chronic) and chronic naproxen use were not regularly associated with false-positive results but did recommend secondary confirmation with GC-MS.

False-positive methadone results with diphenhydramine<sup>15</sup> and doxylamine<sup>16</sup> also have been reported. Daily doses of 100–200 mg of diphenhydramine resulted in false-positive UDS results for three patients.<sup>15</sup> The urine drug concentration needed to show a positive result was 10 mg/L. Doxylamine intoxication resulted in false-positive results for both methadone and opiates when urine samples were checked using EMIT d.a.u. (methadone) and EMIT st (opiates) on admission.<sup>16</sup> Opiates were not detected with Abuscreen radioimmunoassay (Roche Diagnostic Systems, Inc., Montclair, NJ) testing. The urine drug concentrations reported were 50 mg/L (for methadone) and 800 mg/L (for opiates).

A nonprescription nasal inhaler containing the active ingredient *l*-methamphetamine (*l*-desoxyephedrine) yielded false-positive results for amphetamine.<sup>30,35</sup> The extent of the problem was systematically evaluated by Poklis and Moore.<sup>30</sup> In a small study ( $n = 6$ ), four volunteers used the inhaler per manufacturer directions for five consecutive days, while two used twice the recommended dose for three consecutive days. Use of the inhaler according to the prescribing information and double the recommended dose did not have false-positive results using EMIT d.a.u. and EMIT II monoclonal amphet-

amine and methamphetamine assays. However, when the amphetamine class assay (EMIT d.a.u. without the monoclonal designation) was used, both groups produced positive UDS results because the EMIT d.a.u. nonmonoclonal assay detects metabolites of phenylisopropylamine, in addition to *d*-amphetamine and *d*-methamphetamine.

False-positive UDS results for opiates also have been reported with the use of quinolones.<sup>1</sup> Thirteen available agents were tested for false-positive results using five commercially available test kits (AxSym, CEDIA, EMIT II, Roche, and Synchron). The opiate test solution was morphine at concentrations of 0, 225, 300, and 375 ng/mL. Solutions of various concentrations were evaluated with the different assays. If a positive result was obtained, additional dilution was performed to determine the lowest concentration associated with a positive test. In addition, subjects ( $n = 6$ ) were given a single dose of either levofloxacin or ofloxacin, and urine samples were collected over the next 48 hours. At least one assay yielded false-positive results related to the use of nine quinolones. False-positive results were obtained from all six volunteers, with urine samples obtained every 6 hours. Using the EMIT II system, detectable opiate levels ranged from >375 to 225 ng/mL for 20–25 hours. The investigators also recognized the potential additive effects of other substances (specifically poppy seeds) and potential consequences for false-positive results, as did other investigators.<sup>3,21</sup>

False-positive opiate results were reported with the EMIT II for three inpatients (therapeutic doses) and two volunteers (single dose) receiving ofloxacin: urine concentrations of 200 mg/L were sufficient to exceed the morphine threshold of 300 µg/L needed for a false-positive result.<sup>20</sup> No false-positive results were seen in patients receiving ciprofloxacin ( $n = 3$ )

or norfloxacin ( $n = 3$ ). A case report of a false-positive result secondary to gatifloxacin use was reviewed.<sup>21</sup> The patient was participating in a substance abuse residential treatment program, a setting similar to the population that may seek care at the free evening clinic. The urine sample, originally assayed with the Beckman Synchron, was retested with GC-MS; no opiates were detected.

Rifampin is another antiinfective that may be used by medically underserved patients and was reported to be associated with false-positive UDS results. Three cases of false-positive opiate results with rifampin were reported.<sup>36</sup> The original immunoassay used for the first case report was the Syva RapidTest. During follow-up, the Syva RapidTest, Triage, and Genix RapidTech were used on two patients receiving rifampin. One hour post-dose, urine samples assayed with the Syva RapidTest and Genix RapidTech were positive. Confirmatory GC-MS was negative for opiate use. Both of these immunoassays are one-step processes with a cutoff concentration of 300 mg/L.

Another category of medication associated with false-positive UDS results is phenothiazines. One frequently prescribed agent from this class, promethazine, is used for a variety of indications. One large metropolitan emergency department evaluated UDS results for all admitted patients within an 11-month period if two criteria were met: serum promethazine presence and the performance of a UDS ( $n = 22$ ).<sup>17</sup> Of these patients, 36% had false-positive urine results for amphetamines using the EMIT II Plus monoclonal amphetamine/methamphetamine immunoassay. Although this detection product was reported to have greater specificity for amphetamines and methamphetamine, false-positive results were also identified for an antipsychotic (chlorpromazine<sup>37</sup>) and antidepressant (bupropion<sup>9</sup>). In this evaluation, the authors



theorized that the false-positive results were secondary to promethazine metabolites.<sup>17</sup>

The urine samples of 104 subjects were evaluated for false-positive amphetamine/methamphetamine results with the EMIT II monoclonal assay.<sup>37</sup> Subjects' medications included chlorpromazine ( $n = 6$ ) and promethazine ( $n = 20$ ). Negative results were reported with the Syva polyclonal EMIT d.a.u. assay and positive results were observed with the EMIT II assay. Supplement-naive urine samples ( $n = 7$ ) of chlorpromazine intake of  $<100$  mg daily were associated with false-positive results, with one case showing a false positive with a 25-mg daily dosage. Promethazine dosages of  $\geq 50$  mg daily produced positive results in 3 of 18 cases. The investigators theorized that the majority of the results were secondary to phenothiazine structures and that the parent compound, chlorpromazine, may have had some effect.

The potential for psychotropic medications to cause false-positive results for methadone was also evaluated.<sup>10</sup> Kinetics Interaction of Microparticles in Solution (KIMS, Roche), a monoclonal antibody assay, identified possible false-positive results for chlorpromazine, clomipramine, and thioridazine. No cross-reactivity was found for other typical antipsychotics (trifluoperazine, fluphenazine, loxapine) or atypical antipsychotic agents (clozapine, olanzapine, risperidone). No false-positive methadone results were found for citalopram, paroxetine, sertraline, or venlafaxine.<sup>10</sup> Quetiapine was associated with false-positive UDS results for methadone in an adolescent population (testing method not provided).<sup>5</sup> Quetiapine monotherapy in three patients was associated with false-positive results for methadone using the Cobas Integra Methadone II test kit (Roche Diagnostics, USA).<sup>19</sup> However, no information on quetiapine metabolites was included.

Antidepressant use also resulted in false-positive results for amphetamine in two case reports involving bupropion, an aminoketone antidepressant structurally related to phenylethylamines, a class that includes stimulants.<sup>8,9</sup> In these cases, the EMIT U Amp (Dade Behring, Inc., Newark, DE)<sup>8</sup> and EMIT II<sup>9</sup> monoclonal immunoassays were used, but follow-up confirmation with liquid chromatography was negative. This interaction was attributed to one or more of the metabolites; when compared with the calibrating solution of methamphetamine, several of the metabolites, alone and in combination, resulted in concentrations sufficient for positive results.<sup>9</sup> Both the need to include the possible false-positive UDS information in the testing product information<sup>9</sup> and implications for employment or insurance screening were discussed.<sup>8</sup>

False-positive results for benzodiazepines were reported for three inpatients on an adolescent unit prescribed sertraline, a selective serotonin reuptake inhibitor antidepressant.<sup>24</sup> The results were considered valid without a further confirmatory test and therefore caused the loss of privileges and additional consequences for the patient. Daily sertraline doses of  $\geq 150$  mg could result in false-positive UDS results.<sup>24</sup> In a separate evaluation, Nasky and colleagues<sup>25</sup> retrospectively reviewed patients' UDS results that were positive for benzodiazepines while taking sertraline ( $n = 522$ ) and negative with GC-MS. Using this method, 26 (26.5%) of 98 records were identified as false-positive results with  $>69\%$  accuracy of the assay tests (the Aeroset and Architect c8000 Systems, Abbott Laboratories, Irving, TX). This interaction was subsequently addressed in a revised package insert of the tests.

Although less frequently used than other antidepressants, selegiline yielded false-positive amphetamine and methamphetamine results.<sup>38</sup> Se-

legiline is a monoamine oxidase inhibitor used for the treatment of Parkinson's disease. As two of its three major metabolites are *l*-amphetamine and *l*-methamphetamine, a random screen was positive for amphetamine and methamphetamine.<sup>38</sup> GC-MS confirmed the results with high concentrations. A number of follow-up methods determined that only *l*-isomers were involved in the positive UDS results. Additional specimens ( $n = 4$ ) were analyzed, and all samples had methamphetamine concentrations of  $>500$   $\mu\text{g/mL}$ . The authors suggested that the ratio of amphetamine:methamphetamine be identified and that the concentration of specific isomers be considered when interpreting UDS results.

Use of trazodone, a triazolopyridine antidepressant, yielded one false-positive amphetamine result.<sup>26</sup> No quantification information was included in the report. In addition, one report of a false-positive result associated with a trazodone overdose was found.<sup>33</sup> Use of venlafaxine, a serotonin and norepinephrine reuptake inhibitor, resulted in a number of false-positive reports for phenacyclidine.<sup>27-29</sup> Although venlafaxine is structurally dissimilar to phenacyclidine, the combination of parent compound and active metabolite, primarily *O*-desmethylvenlafaxine, was theorized to cause false-positive results secondary to cross-reactivity with the antiphenacyclidine antibodies.<sup>29</sup> Testing was performed with the following systems: Syva RapidTest d.a.u.,<sup>29</sup> AxSym (Abbott Laboratories),<sup>27</sup> and Instant-View (Alpha Laboratories) multidrug screen urine test.<sup>28</sup>

False-positive results for methadone with verapamil metabolites were also reported.<sup>2</sup> Subsequent to this report, the manufacturer confirmed the results and included this product in its monoclonal antimethadone antibody screen.<sup>39</sup> No additional reports of false-positive results with verapamil were found.

## Discussion

The most commonly used UDS tests are immunoassays, as they allow large-scale screenings with rapid detection at minimal expense.<sup>40</sup> The disadvantage of immunoassays, when compared with the use of GC-MS (“the gold standard”), is false-positive results.<sup>7</sup> A false-positive result for individuals with court-ordered or work-related screening can lead to legal interventions, workplace disruptions, or questions of honesty. A more specific confirmatory test should be conducted prior to releasing the initial screening results.<sup>8</sup>

Accounts of false-positive UDS results for drugs of abuse have been reported with a number of rapid-screening immunoassay products. After receiving positive results for illicit or abused substances, additional confirmatory testing was done in some cases. This included more detailed patient interviews and secondary analysis with GC-MS to more precisely identify the offending substances. Awareness of the potential for false-positive results and confirmatory follow-up information are particularly important for the patients who seek care at the Bedlam evening clinic. Patients may be unaware of potential false-positive reactions when they use prescribed medications and of the correct follow-up procedures to properly resolve the situation. Health care delivery may be provided for the working poor by additional resources, such as the Department of Health or other service providers.

UDS sample timing was found to be important in several of the reports.<sup>2,3,15,17,27</sup> In other reports, the presence of metabolites with different structures, pharmacokinetics, or pharmacodynamic properties may have been factors in the results.<sup>10,26</sup> Reagent specificity or sensitivity is another concern.<sup>1,6,41</sup> Patient-specific factors, such as the physiological effects of weight or diet (as they apply

to urine acidity or alkalinity) were not included in this review of formulary agents. Based on the reports reviewed, no single reagent was identified with false-positive results. The ranges of the results were developed for the adult, not pediatric, population.<sup>32</sup>

With the increased availability of onsite drug testing and the variety of products associated with reports of false-positive results in the literature, confirmation of results is needed. Failure to follow up to determine if a false positive may have occurred could result in unnecessary adverse consequences for the patient (e.g., incarceration, employment denial, loss of privileges).

## Conclusion

A number of routinely prescribed medications have been associated with triggering false-positive UDS results. Verification of the test results with a different screening test or additional analytical tests should be performed to avoid adverse consequences for the patients.

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