False-Positive Urine Drug Screens: Clinical Challenges and Confirmatory Testing

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Urine drug screening (UDS) is a cornerstone of clinical practice for detecting drugs of abuse. In practice, UDS results often guide critical treatment decisions. These results may also be used by legal authorities (e.g., law enforcement) and employers, potentially influencing legal or employment outcomes (1). Yet clinicians may place too much trust in an inherently imperfect method.

Too often, clinicians interpret a "positive" UDS as definitive proof of substance use, yet the reality is far more complex. Immunoassays, the rapid, qualitative tests most commonly used for urine screening, are susceptible to both false-positive and false-negative results (2,3). Commonly prescribed medications can trigger false-positive results that may alter treatment plans, whereas false-negative results can lead to undetected misuse (3-5).

Many apparent "positive" amphetamine or opioid results may actually reflect routine medications rather than illegal use or abuse (3). Therefore, it is important to interpret urine drug tests with caution and to advocate for confirmatory testing before drawing any conclusions. Vigilance is essential—not only to avoid mislabeling patients but also to uphold the integrity of clinical decision-making.

Problems with Immunoassays

Most rapid, on-site urine drug screens utilize commercial immunoassays that detect drug metabolites through specific antigen-antibody interactions (1). Structurally similar compounds, prescription medications, over-the-counter drugs, or even metabolites can cross-react with the antibodies, leading to false-positive results (6,7).

Some well-known examples include:

- Ranitidine (largely withdrawn) → false positive for amphetamines (6).
- Bupropion → false positive for amphetamines (7).
- Sertraline → false-positive benzodiazepine results (8).
- Zonisamide → false-positive benzodiazepines (9).
- Quetiapine → false-positive for tricyclic antidepressants (TCAs) or for methadone (10).
- Fluoroquinolones → false positives for opioids and amphetamines (11).
- Dextromethorphan → false-positive PCP (phencyclidine) (12).
- Diphenhydramine → false-positive opioids or methadone (13).
- Ibuprofen → historically linked to false-positive cannabinoids or barbiturates in older assays (14).
- Rifampin and rifampicin → false-positive opioids (15).

Recognizing that many medications can trigger inaccurate test results, UDS should be used solely as a screening tool, not a diagnostic endpoint (3).

Consequences That Extend Beyond the Lab Result

In clinical settings, an incorrectly interpreted drug screen can lead to incorrect diagnoses, discontinuation of needed medications, or unnecessary referrals (15,16). Furthermore, false-positive test results can harm the provider-patient relationship. Despite having taken medications as prescribed, the patient(s) may be thought of or labeled as "non-adherent" or "drug-seeking" (15). Obviously, such labeling carries serious risks. Beyond the clinical setting, false-positive UDS results can also have broad consequences, affecting employment, housing eligibility, and legal matters.

Given these risks, clinicians should maintain a critical approach to unexpected UDS results. When a positive screen does not correspond with a patient's history or observed behavior, the response should emphasize careful assessment rather than discipline. Confirmatory testing with gas chromatography–mass spectrometry (GC-MS) remains the criterion standard, as it eliminates the cross-reactivity intrinsic to immunoassays (15). It should be noted that Confirmatory testing is often underutilized, likely due to cost, limited availability, or lack of institutional support (16). It is essential to establish systems that automatically initiate confirmatory testing, particularly when: 1) the patient denies drug use and has a reliable history, 2) the medication list includes agents known to cause cross-reactivity, and 3) the UDS result could influence clinical decisions, legal proceedings, or employment outcomes. Confirmatory testing serves as a critical safeguard against stigma, diagnostic errors, and unfair treatment in clinical practice.

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Need for Multidisciplinary Approach

It is important to recognize the critical role of pharmacists and nurses, alongside ordering physicians and other providers, in the interpretation of UDS results. Pharmacists play a crucial role in flagging medications with potential for false positives and should regularly review this during medication reconciliation and team meetings (16,17). Nurses can serve as first-line educators and advocates, especially when patients express confusion or fear over test results (18). Electronic health records can be optimized to include alerts for medications with known cross-reactivity, for instance, a flag noting when a patient is taking a drug that warrants cautious interpretation of UDS results.

Conclusion

While UDS is a valuable tool, it is not completely reliable and may yield false-positive results for drugs of abuse. Clinicians must interpret UDS results with caution and a critical eye. It is essential to uphold the principles of evidence-based practice, not only when it is convenient, particularly when the impact on patient care is greatest. Whenever indicated, confirmatory testing should be pursued, as it represents both best practice and a fundamental professional responsibility.

Conflict of Interest

The author has no conflict of interest to declare.

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