A Review of the Methods, Interpretation, and Limitations of the Urine Drug Screen

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Abstract: Toxicology screens are used to detect the presence of prescription, nonprescription, or illicit substances. These tests are used in emergency situations to detect intentional or accidental overdose, to monitor drug dependency, and to screen for medical or legal purposes. An initial immunoassay reports qualitative results based on established cut-off concentrations. As a screening test, the initial immunoassay is less sensitive and therefore must be interpreted in the context of confounding variables such as the testing method, the substance being screened, and patient-specific characteristics. Either gas chromatography or high-performance liquid chromatography can be used to confirm positive results.

Toxicology screens are commonly used in various health care settings. These screening tests can be broadly defined as an examination of a biological specimen to detect the presence of a specific chemical substance or its metabolites. Specimens such as urine, hair, saliva, sweat, and blood may be tested. This article discusses the urine toxicology screen or urine drug screen (UDS), as this is the most frequently used in clinical practice.

Methods of Toxicology Screening

Biological Specimen

The source of the biological specimen used in toxicology screens affects certain characteristics of these tests, including the period of detection. This period can be defined as the duration of time elapsed from when a substance was last used (assuming typical use) that one could expect to still obtain a positive qualitative result. In general, hair specimens have an increased period of detection compared to other biological specimens, with some substances being detected up to 90 days after last use. Saliva testing is considered to have the shortest period of detection, with most substances only being recognized if used within the past 24 to 48 hours.

However, patients who extensively use substances at higher quantities or frequencies than typical use may have prolonged periods of detection regardless of the biological specimen. Providers must also account for the specific substance being screened, because certain characteristics like pharmacokinetic parameters may alter the usual period of detection. Overall, the UDS is the most frequently used method based on convenience, cost, and accessibility. The basic differences in the periods of detection in the UDS based on the substance being screened are summarized in Table 1.

Clinical Use

Urine drug screens can be used for various reasons. In certain clinical scenarios, a toxicology screen may assist practitioners in narrowing their initial differential diagnosis list. Common reasons that toxicology screens are ordered include emergency situations such as traumas, seizures, or significant altered mental status; concern for intentional or accidental overdose; monitoring drug dependency; and screening for medical or legal purposes.

Prior to ordering these screening tests, it is important to consider their purpose.

A 2009 review article analyzed 1405 patients who presented to the emergency
department to determine how a UDS affects patient management in the emergency department. The conclusion of the reviewers was that UDSs in the emergency department did not significantly impact patient management during their stay. Therefore, the authors recommended against routine UDSs in this setting.

Regarding the UDS as a screen for opiate use, the American Pain Society refers to the UDS as a potential method to monitor chronic opiate use in noncancer patients. However, they also note the limitations of most of the evidence supporting the accuracy of UDSs in this setting. In 2010, a systematic review specifically attempted to address the question of whether routine UDSs deterred abuse of opiates. Reviewers found 11 observational studies that met inclusion criteria and, based on these trials, concluded there was a modest, nonstatistically significant decrease in opiate abuse with routine UDSs. Four of these studies compared specific monitoring treatment agreements, some of which included routine UDSs, to a control group and found the incidence of opiate misuse had an absolute relative risk reduction from 7% to 23% with the monitored group. It is important for providers to recognize the benefits and limitations of the UDS to use it appropriately in clinical practice. Providers should understand that the UDS is a screening test and should not be considered diagnostic.

### Screening Techniques

Clinical laboratories may use various testing methods, but the most common techniques include the spot test, spectrochemical test, immunoassay, and chromatographic testing. Spot tests are simple tests that result in a color change due to a chemical reaction. These tests, although rapid, have for the most part fallen out of favor due to the subjective interpretation of the change in color resulting in decreased sensitivity.

Spectrochemical testing methods like spot tests also analyze a chemical reaction. A spectrophotometer measures the changes in light absorption throughout the course of the chemical reaction in rate spectrophotometry. This serves to quantitatively measure light absorption at different wavelengths to identify various substances. The issue with this screening method is the low sensitivity, in that other substances that either alter the chemical reaction or alter light absorption may confound the result. Based on the limitations of both the spot and spectrochemical tests, the immunoassay and chromatographic testing methods are typically the most used.

The UDS, like most toxicology screening methods, is part of a 2-step process that incorporates the immunoassay and the chromatographic testing method. The first step is the immunoassay, which works by either competitive or noncompetitive binding. Urine drug screens typically work competitively, which means the drug substance itself displaces some previously labeled substance originally on the antibody.

The most frequently used UDSs work by homogenous immunoassay, which, rather than detecting for the presence of the unbound labeled substance, compares the concentration of the labeled free vs the concentration of the labeled attached substance. Types of homogeneous immunoassays include enzyme-multiplied immunoassay technique, fluorescence polarization immunoassay, and radioimmunoassay. Immunoassays are sensitive, fairly inexpensive tests and are relatively easy to perform because they are easily collected and automated. Poor sensitivity is a concern with the first step of the UDS process, so a confirmatory test is recommended for immunoassay positive results.

Confirmatory tests are frequently done via the second step, gas chromatography–mass spectrometry or high-performance liquid chromatography. Chromatography tests work by separation of substances into a mobile and a stationary phase. The amount of time in the mobile phase correlates to a specific length that is reproducible under specific conditions, which are mimicked in the UDS. These testing methods are more cumbersome than the other methods; however, they are the most sensitive and specific tests to help exclude false positive results. Providers should know their clinical laboratory protocols because depending on the policy, confirmatory tests may or may not be automatic for positive results. If these tests are not routine, providers may have to specifically request a confirmatory test.

### Interpretation of Results

#### Qualitative Reporting

The first thing to consider when interpreting UDS results is what the qualitative result from the immunoassay really indicates. Positive and negative results are differentiated based on established cut-off values. This means that substances above a certain concentration in the UDS correlate with a positive result, and if the concentration is less than the established value, a negative result is reported. Therefore, a negative result for a particular substance does not necessarily correlate to it not being present, but rather the
concentration present is less than the established cut-off value.

Furthermore, these values are specific to the substance being tested, the biological specimen, and the testing device. Something else to consider is that clinical laboratories are able to set their own limits of detection. For example, the Department of Health and Human Services (DHHS) increased the cut-off values for opiates in workplace UDSs from 300 ng/mL to 2000 ng/mL in 1998; however, some laboratories still use the more sensitive cut-off value.3,11

Common False Positives

When health care practitioners consider performing a UDS on a patient, it is essential to obtain an accurate and detailed medication history, because many commonly used medications are known to contribute to false positive results. Table 2 summarizes the substances that have been shown to result in false positive UDS results and the illicit substance implicated as being positive.3,6

Many drug classes, both prescription and non-prescription, have been found to contribute to false positive UDS results, including antihistamines, antidepressants, antipsychotics, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs).3,6 This further demonstrates why a thorough medication history is essential prior to screening patients. The extent of agents reported to cause false positive results demonstrates the lack of sensitivity in the initial UDS immunoassay method. This underlines the need for confirmatory testing methods that can rule out the majority of false positive results.2

The most common substances reported as having false positive results were amphetamines and methamphetamines.3,6 The majority of these false positives are caused by other stimulant substances or compounds that are structurally similar to amphetamine or methamphetamine. More than 30 substances have been reported to interfere with this immunoassay.3,6 This includes nonprescription, prescription, and herbal products. For example, structurally similar compounds such as brompheniramine, trazodone, and promethazine have all resulted in false positives.6 High doses of ranitidine (ie, >150 mg/day) taken relatively close to screening (ie, <9 hours) have also been reported as false positives for amphetamine or methamphetamine on UDSs.6,12,13

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The fact that a wide variety of agents may lead to false positive UDS results is significant. The ability of nonprescription products to interfere with the tests’ validity may be particularly problematic. Patients may not recognize the importance of these medications when reporting their prescriptions; therefore, they may not discuss the use of these medications with their health care providers.

If a patient had recently developed a cough, he may not discuss his use of nonprescription cough and cold preparations because he may not recognize its relevance. However, brompheniramine, guaifenesin, and phenylephrine, which are all commonly found in nonprescription cough and cold products, have been reported as causing false positive amphetamine or methamphetamine UDSs.6,13 In addition, substances such as dextromethorphan, a nonprescription cough suppressant, and diphenhydramine, a nonprescription antihistamine, have been linked to false positive phencyclidine (PCP) UDSs.6 Therefore, providers should ask patients about their use of nonprescription and herbal products prior to drug screening to get a complete medication history.

Also of note, certain NSAIDs have been reported to cause false positive UDS results. Specifically, naproxen, fenoprofen, and ibuprofen have been linked to cannabinoid, barbiturate, and PCP positive tests.3,6,14 Oxaprozin, an NSAID indicated for rheumatic arthritis and osteoarthritis, includes a warning of the potential for false positive UDSs in its prescribing information.15

Remember the False Negatives

Although negative results may occur due to concentrations less than the cut-off value, it is also possible that the UDS is unable to or does not routine-

Table 2

<table>
<thead>
<tr>
<th>Substance</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>Amphetamine/methamphetamine</td>
<td>Amantadine, brompheniramine, bupropion, chlorpromazine, desipramine, dextroamphetamine, euphedrine, isomethetene, labetalol, methylene dioxymethamphetamine, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, promethazine, pseudoephedrine, ranitidine, selegiline, thioridazine, trazodone, trimethobenzamide, trimipramine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Fenoprofen, ibuprofen, naproxen</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Oxaprozin, sertraline</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Dronabinol, efavirenz, fenoprofen, ibuprofen, naproxen, pantoprazole</td>
</tr>
<tr>
<td>Opiates</td>
<td>Dextromethorphan, diphenhydramine, gatifloxacin, ibruloxacin, rifampin, verapamil</td>
</tr>
<tr>
<td>Methadone</td>
<td>Clomipramine, chlorpromazine, diphenhydramine, doxylamine, quetiapine, thioridazine, verapamil</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Dextromethorphan, diphenhydramine, doxylamine, ibuprofen, imipramine, ketamine, meperidine, mesoridazine, thioridazine, tramadol, venlafaxine</td>
</tr>
</tbody>
</table>

Abbreviation: UDS, urine drug screen.
**THE BOTTOM LINE**

- Biological specimens used to perform toxicology screens can include urine, hair, saliva, sweat, and blood; however, the urine drug screen (UDS) is the most common.
- The UDS is a screening test and as such lacks sensitivity; for this reason, confirmation of positive results by gas chromatography-mass spectrometry or high-performance liquid-chromatography is recommended.
- A variety of drug classes have been reported as the etiology of false positive urine drug screens. These classes include commonly utilized prescription and non-prescription drugs such as antihistamines, antidepressants, antipsychotics, and non-steroidal anti-inflammatory drugs (NSAIDs).
- Providers should consider variables which may affect UDS results; which includes characteristics of the method of screening, the substance being analyzed, and the patient being screened.

**Pharmacokinetic Considerations**

Pharmacokinetic properties of the substances being screened may affect the UDS results. Absorption, distribution, metabolism, and elimination can all have a potential impact. Because the UDS detects a cutoff concentration in the urine, the rate and extent of absorption may affect the outcome. The rate of absorption varies based on the route of administration. Gastrointestinal, inhalational, or intravenous administration have variable rates of absorption, which may change the time to peak concentration and therefore the onset of action. In general, intravenous administration has the fastest rate of absorption, quickest time to peak, and quickest onset of action, which may affect detection in the UDS. Absorption, which can be defined as the extent of a substance that is present physiologically after oral ingestion, can affect the extent of absorption. Substances that are less bioavailable will have decreased concentrations throughout the body, including in the urine.

Regarding distribution, lipophilic agents generally tend to have better central nervous system and tissue penetration, whereas hydrophilic substances tend to concentrate in the urine. This may alter the concentration detected in a UDS and ultimately affect the results. The volume of distribution and extent of protein binding may contribute to UDS interpretation as well. Only unbound drugs are distributed and eliminated; therefore, decreased protein binding may result in shorter periods of detection through quicker elimination rates.

Metabolism and elimination are also important pharmacokinetic parameters to consider in the substance being screened. Screening tests may be designed to detect particular metabolites; therefore, the ability to produce specific metabolites, as well as the presence or absence of active metabolites, is important.

Regarding elimination, the half-life of the substance being screened is important because it directly correlates to the period of detection. The rate of elimination may be affected by the integrity of renal or hepatic function, the potential for saturation of enzyme processes and thereby the accumulation of these substances, and the competition for elimination by other substances.

Providers should consider the saturation of these processes, which may occur at higher concentrations and result in nonlinear pharmacokinetic parameters. The principle of pharmacokinetics at concentrations that result in toxicity is termed toxicokinetics. These elevated concentrations can affect the normal absorption, distribution, metabolism, and elimination of substances screened in a UDS. This principle is demonstrated in that chronic, frequent, heavy users of illicit substances typically have prolonged periods of detection. In a UDS, PCP is generally detected for 4 to 7 days; however, with chronic, frequent users, periods of detection can be up to 30 days.

In addition to the pharmacokinetic parameters of the substance, patient-specific factors may contribute to the absorption, distribution, metabolism, and elimination of substances screened in UDSs. A patient’s demographic characteristics such as age, weight, and sex should be considered when interpreting UDS results. Obese patients with increased adipose tissue may have increased distribution of lipophilic substances. Patients with critical illness have altered pharmacokinetic parameters, such as renal insufficiency, and therefore may...
have inadequate filtering and concentrating of drug substances in the urine. Changes from normal urinary pH can also affect the renal elimination of weak acids or bases due to changes in percent ionization. For example, normal urine pH is 4 to 8, but methamphetamine, which is a weak base, will have increased renal elimination with acidification of the urine due to increased ionization and therefore decreased reabsorption. Patient-specific parameters, such as these mentioned, should be considered by providers to appropriately interpret UDSs.

CONCLUSION

Toxicology screening may provide useful, objective information to clinicians to more effectively treat patients. However, the limitations of these screening methods, especially UDSs, should be recognized for appropriate analysis of results. Positive immunoassay results in the UDS should be confirmed through a more sensitive chromatography testing method. Furthermore, it is essential to consider confounding variables such as the potential for false positives, substance specific pharmacokinetic parameters, and patient demographics when interpreting UDS results. There is clinical use to the UDS, but to be effectively used, it must be ordered and the results must be analyzed in the context of its limitations.

REFERENCES