Urine drug tests:
How to make the most of them

Effective use of UDTs requires carefully interpreting the results, and modifying treatment accordingly

Urine drug tests (UDTs) are useful clinical tools for assessing and monitoring the risk of misuse, abuse, and diversion when prescribing controlled substances, or for monitoring abstinence in patients with substance use disorders (SUDs). However, UDTs have been underutilized, and have been used without systematic documentation of reasons and results. In addition, many clinicians may lack the knowledge needed to effectively interpret test results. Although the reported use of UDTs is much higher among clinicians who are members of American Society of Addiction Medicine (ASAM), there is still a need for improved education.

The appropriate use of UDTs strengthens the therapeutic relationship and promotes healthy behaviors and patients’ recovery. On the other hand, incorrect interpretation of test results may lead to missing potential aberrant behaviors, or inappropriate consequences for patients, such as discontinuing necessary medications or discharging them from care secondary to a perceived violation of a treatment contract due to unexpected positive or negative drug screening results. In this article, we review the basic concepts of UDTs and provide an algorithm to determine when to order these tests, how to interpret the results, and how to modify treatment accordingly.

Urine drug tests 101

Urine drug tests include rapid urine drug screening (UDS) and confirmatory tests. Urine drug screenings are usually based on various types of immunoassays. They are fast, sensitive, and cost-effective. Because immunoassays are antibody-mediated, they have significant
false-positive and false-negative rates due to cross-reactivity and sensitivity of antibodies. For example, antibodies used in immunoassays to detect opioids are essentially morphine antibodies, and are not able to detect semisynthetic opioids or synthetic opioids (except hydrocodone). However, immunoassays specifically developed to detect oxycodone, buprenorphine, fentanyl, and methadone are available. On the other hand, antibodies can cross-react with molecules unrelated to proto-medicines or drug metabolites, but with similar antigenic determinants. For example, amphetamine immunoassays have high false-positive rates with many different classes of medications or substances.

Urine drug tests based on mass spectrometry, gas chromatography/mass spectrometry (GC/MS), and liquid chromatography/mass spectrometry (LC/MS) are gold standards to confirm toxicology results. They are highly sensitive and specific, with accurate quantitative measurement. However, they are more expensive than UDS and usually need to be sent to a laboratory with capacity to perform GC/MS or LC/MS, with a turnaround time of up to 1 week. In clinical practice, we usually start with UDS tests and order confirmatory tests when needed.

**Factors that can affect UDT results**

In addition to knowing when to order UDT, it is critical to know how to interpret the results of UDS and follow up with confirmatory tests when needed. Other than the limitations of the tests, the following factors could contribute to unexpected UDT results:

- the drug itself, including its half-life, metabolic pathways, and potential interactions with other medications
- how patients take their medications, including dose, frequency, and pattern of drug use
- all the medications that patients are taking, including prescription, over-the-counter, and herbal and supplemental preparations
- when the last dose of a prescribed controlled substance was taken. Always ask when the patient’s last dose was taken before you consider ordering a UDT.
**Figure 1**

Metabolic pathways of commonly used benzodiazepines

*Drugs in bold are commonly used benzodiazepines

CYP: cytochrome P450

**Source**: Reference 14

**Figure 2**

Metabolic pathways of commonly used opioids

*Dashed lines indicate minor pathways. Drugs in bold are commonly used opioids

CYP: cytochrome P450; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine

**Source**: Reference 15
### Clinical Point

For patients taking medications that are undetectable by UDS, consider ordering confirmatory tests at least once to ensure compliance.

### Table

Commonly seen false positives and false negatives in urine drug screens

<table>
<thead>
<tr>
<th>Immunoassays</th>
<th>Detecting drugs/metabolites</th>
<th>Other drugs detected in the same class</th>
<th>Potential false positive(^a)</th>
<th>Potential false negative(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine(^b)</td>
<td>Amphetamine</td>
<td>Dextroamphetamine, lisdexamphetamine</td>
<td>Bupropion, trazodone, desipramine, doxepin, labetalol, metformin, promethazine, ephedrine, pseudoephedrine, phentermine, atomoxetine, ranitidine</td>
<td>None known</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam</td>
<td>Oxazepam, temazepam, flurazepam, chlordiazepoxide, midazolam (±), triazolam (±), lorazepam (±), alprazolam (±)</td>
<td>Sertraline, oxaprozin, efavirenz</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Buprenorphine</td>
<td>Morphine, methadone, codeine, tramadol</td>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Benzoylcegonine</td>
<td>None</td>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>9-carboxy-THC</td>
<td>Efavirenz, ibuprofen, naproxen, dronabinol</td>
<td>Nabilone, synthetic and designer cannabinoids (spice, K2)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone</td>
<td>Antipsychotics (quetiapine, thioridazine, chlorpromazine), verapamil, diphenhydramine</td>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphine</td>
<td>Codeine, heroin, hydrocodone/hydmorphone (±)</td>
<td>Quinolones, naltrexone, diphenhydramine, rifampicin</td>
<td>Oxycodone/oxymorphone, fentanyl, methadone, buprenorphine, tramadol, meperidine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone</td>
<td>None known</td>
<td>None known</td>
<td></td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Phencyclidine</td>
<td>Venlafaxine, lamotrigine, ibuprofen, dextromethorphan, bath salt, tramadol, zolpidem</td>
<td>None known</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The potential false positives and false negatives listed do not indicate that the drug(s) will show or not show every time for every patient in every immunoassay.

\(^b\)Methylphenidate will not show positive as amphetamine in both immunoassay and confirmatory tests.

\(±\): The medication can be detected by immunoassay, but not very consistently; THC: tetrahydrocannabinol

**Source:** References 16-21
To help better understand UDT results, *Figure 1* (page 13) and *Figure 2* (page 13) demonstrate metabolic pathways of commonly used benzodiazepines and opioids, respectively. There are several comprehensive reviews on commonly seen false positives and negatives for each drug or each class of drugs in immunoassays.\(^{16-21}\) Confirmatory tests are usually very accurate. However, chiral analysis is needed to differentiate enantiomers, such as methamphetamine (active R-enantiomer) and selegiline, which is metabolized into L-methamphetamine (inactive S-enantiomer).\(^{22}\) In addition, detection of tetrahydrocannabivarin (THCV), an ingredient of the cannabis plant, via GC/MS can be used to distinguish between consumption of dronabinol and natural cannabis products.\(^{23}\) The *Table*\(^{16-21}\) (page 14) summarizes the prototype agents, other detectable agents in the same class, and false positives and negatives in immunoassays.

### Interpreting UDT results and management strategies

Our *Algorithm* (page 16) outlines how to interpret UDT results, and management strategies to consider based on whether the results are as expected or unexpected, with a few key caveats as described below.

**Expected results**

If there are no concerns based on the patient’s clinical presentation or collateral information, simply continue the current treatment. However, for patients taking medications that are undetectable by UDS (for example, regular use of clonazepam or oxycodone), consider ordering confirmatory tests at least once to ensure compliance, even when UDS results are negative.

**Unexpected positive results, including the presence of illicit drugs and/or unprescribed licit drugs**

**Drug misuse, abuse, or dependence.** The first step is to talk with the patient, who may acknowledge drug misuse, abuse, or dependence. Next, consider modifying the treatment plan; this may include more frequent monitoring and visits, limiting or discontinuing prescribed controlled substances, or referring the patient to inpatient or outpatient SUD treatment, as appropriate.

### Interference from medications or diets

One example of a positive opioid screening result due to interference from diet is the consumption of foods that contain poppy seeds. Because of this potential interference, the cutoff value for a positive opioid immunoassay in workplace drug testing was increased from 300 to 2,000 ug/L.\(^{24}\) Educating patients regarding medication and lifestyle choices can help them avoid any interference with drug monitoring. Confirmatory tests can be ordered at the clinician’s discretion. The same principle applies to medication choice when prescribing. For example, a patient taking bupropion may experience a false positive result on a UDS for amphetamines, and a different antidepressant might be a better choice (*Box 1*, page 17).

**Urine sample tampering.** Consider the possibility that urine samples could be substituted, especially when there are signs or indications of tampering, such as a positive pregnancy test for a male patient, or the presence of multiple prescription medications not prescribed to the patient. If there is high suspicion of urine sample tampering, consider observed urine sample collection.

**When to order confirmatory tests for unexpected positive results.** Order a confirmatory test if a patient adamantly denies taking the substance(s) for which he/she has screened positive, and there’s no other explanation for the positive result. Continue the patient’s current treatment if the confirmatory test is negative. However, if the confirmatory test is positive, then modify the treatment plan (*Algorithm*, page 16).

**Special circumstances.** A positive opioid screen in a patient who has been prescribed a synthetic or semisynthetic opioid indicates the patient is likely using opioids other than the one he/she has been prescribed. Similarly, clonazepam is expected to be negative in a benzodiazepine immunoassay. If such testing is positive, consider the possibility that the patient is taking

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A patient taking bupropion may experience a false-positive result on a UDS for amphetamines.
other benzodiazepines, such as diazepam. The results of UDTs can also be complicated by common metabolites in the same class of drugs. For example, the presence of hydromorphone for patients taking hydrocodone does not necessarily indicate the use of hydromorphone, because hydromorphone is a metabolite of hydrocodone (Figure 2, page 13).

Unexpected negative results
Prescribed medications exist in low concentration that are below the UDS detection threshold. This unexpected UDS result could occur if patients:

- take their medications less often than prescribed (because of financial difficulties or the patient feels better and does not think he/she needs it, etc.)
- hydrate too much (intentionally or unintentionally), are pregnant, or are fast metabolizers (Box 2, page 18)
- take other medications that increase the metabolism of the prescribed medication.

Further inquiry will clarify these concerns. Clinicians should educate patients and manage accordingly. Confirmatory tests may be ordered upon clinicians’ discretion.

Urine sample tampering. Dilution or substitution of urine samples may lead to
unexpected negative results. Usually, the urine sample will have abnormal parameters, including temperature, pH, specific gravity, urine creatinine level, or detection of adulterants. If needed, consider observed urine sample collection. Jaffee et al.25 reviewed tampering methods in urine drug testing.

Diversion or binge use of medications. If patients adamantly deny diverting or binge using their medication, order confirmatory tests. If the confirmatory test also is negative, modify the treatment plan accordingly, and consider the following options:

- adjust the medication dosage or frequency
- discontinue the medication
- conduct pill counts for more definitive evidence of diversion or misuse, especially if discontinuation may lead to potential harm (for example, for patients prescribed buprenorphine for opioid use disorder).

When to order confirmatory tests for unexpected negative results. Because confirmatory tests also measure drug concentrations, clinicians sometimes order serial confirmatory testing to monitor lipophilic drugs after a patient reports discontinuation, such as in the case of a patient using marijuana, ketamine, or alprazolam. The level of a lipophilic drug, such as these 3, should continue to decline if the patient has discontinued using it. However, because the drug level is affected by how concentrated the urine samples are, it is necessary to compare the ratios of drug levels over urine creatinine levels.26 Another use for confirmatory-quantitative testing is to detect “urine spiking,”27,28 when a patient adds an unconsumed drug to his/her urine sample to produce a positive result without actually taking the drug (Box 3, page 18).
When to consult lab specialists

Because many clinicians may find it challenging to stay abreast of all of the factors necessary to properly interpret UDT results, consulting with qualified laboratory professionals is appropriate when needed. For example, a patient was prescribed codeine, and his UDTs showed morphine as anticipated; however, the prescribing clinician suspected that the patient was also using heroin. In this case, consultation with a specialist may be warranted to look for 6-mono-acetylmorphine (6-MAM, a unique heroin metabolite) and/or the ratio of morphine to codeine.

In summary, UDTs are important tools to use in general psychiatry practice, especially when prescribing controlled substances. To use UDTs effectively, it is essential to possess knowledge of drug metabolism and the limitations of these tests. All immunoassay results should be considered as presumptive, and confirmatory tests are often needed for making treatment decisions. Many clinicians are unlikely to possess all the knowledge needed to correctly interpret UDTs, and in some cases, communication with qualified laboratory professionals may be necessary. In addition, the patient’s history and clinical presentation, collateral information, and data from prescription drug monitoring programs are all important factors to consider.

The cost of UDTs, variable insurance coverage, and a lack of on-site laboratory services can be deterrents to implementing UDTs as recommended. These factors vary significantly across regions, facilities, and insurance providers (see Related Resources, page 20). If faced with these issues and you expect to often need UDTs in your practice, consider using point-of-care UDTs as an alternative to improve access, convenience, and possibly cost.

References

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Top Line

Urine drug tests (UDTs) should be standard clinical practice when prescribing controlled substances and treating patients with substance use disorders in the outpatient setting. Clinicians need to be knowledgeable about the limitations of UDTs, drug metabolism, and relevant patient history to interpret UDTs proficiently for optimal patient care. Consult laboratory specialists when needed to help interpret the results.

Related Resources

Drug Brand Names
- Alprazolam - Xanax
- Amphetamine - Adderall
- Atomoxetine - Strattera
- Buprenorphine - Subutex
- Buprenorphine/naloxone - Suboxone, Zubsolv
- Bupropion - Wellbutrin, Zyban
- Chloralhydrate - Librium
- Chlorpromazine - Thorazine
- Clonazepam - Klonopin
- Desipramine - Norpramin
- Dextroamphetamine - Dexedrine, ProCentra
- Dexamphetamine - Dexedrine, ProCentra
- Diazepam - Valium
- Doxepin - Silenor
- Drinabinol - Marinol
- Efavirenz - Sustiva
- Ephedrine - Akovaz
- Fentanyl - Actiq, Duragesic
- Flurazepam - Dalmane
- Hydrocodone - Hisingla, Zohydro ER
- Hydromorphone - Dilaudid, Exalgo
- Labelalol - Normodyne, Trandate
- Lamotrigine - Lamictal
- Lisexdexamfetamine - Vyvanse
- Lithium - Eskalith, Lithobid
- Lorazepam - Ativan
- Meperidine - Demerol


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When needed, consult qualified laboratory specialists to help interpret UDT results