Strategies for preventing and detecting false-negatives in urine drug screens

Hassan I. Khidr, MBBcH, MD, and Cuneyt Tegin, MD

Urine drug screening (UDS) is an important tool in emergency settings and substance abuse or pain management clinics. According to the 2015 National Survey on Drug Use and Health, 9.2% of individuals age ≥12 used an illicit drug other than marijuana within the previous year.[1]

There are 2 types of UDS: gas chromatography–mass spectroscopy (GC-MS) and enzymatic immunoassay (EIA). A GC-MS uses a 2-step mechanisms to detect chemical compounds. First the GC separate the illicit substance into molecules, which is then introduced to the MS, which then separates compounds depending on their mass and charge using magnetic fields.[2,3] Although GC-MS is a more definitive means to confirm the presence of a specific drug, it rarely is used in clinical settings because it is expensive and time-consuming.

EIA is an anti-drug antibody added to the patient's urine that causes a positive indicator reaction that can be measured.[2,3] It is a rapid, accurate, and cost-effective way of detecting illicit substances.[4] However, there are limitations to EIAs used in most hospital laboratories.

Limitations of EIAs

Timing. Results of the drug screen depend on the time and frequency of drug use (***Table 1, page e2***).[5]

Sensitivity. The immunoassay methods used vary in their ability to detect substances and depend on the test's sensitivity; however, most of these versions have high sensitivity for detecting many illicit substances.[4]

Specificity and cross-reactivity. Unfortunately, many drugs, such as opioids, amphetamines, and commonly prescribed medications, exhibit cross-reactivity that can produce false-positive results (***Table 2, page e2***).[5,6]

Synthetic cannabinoids, such as "spice" and cathinones, also known as "bath salts," cannot be detected with standard UDS. However, some newer EIA kits can detect synthetic cannabinoids but do not detect newer designer drugs.[7] Detection of specific cathinones by EIA is not yet available.[7]

Preventing false-negatives

Substance abusing individuals could try to avoid detection of illicit drug use by using the following techniques:

- **In vivo** methods, such as drinking a large amount of water or using herbal products, can lead to false-negative results because of dilution.[8]

continued

LET YOUR VOICE BE HEARD

Current Psychiatry invites psychiatry residents to share their views on professional or clinical topics for publication in Residents' Voices. E-mail residents@currentpsychiatry.com for author guidelines.

Hassan I. Khidr, MBBcH, MD

Cuneyt Tegin, MD

Drs. Khidr and Tegin are PYG-3 Psychiatry Residents, University of Louisville, Louisville, Kentucky.

Disclosures
The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Table 1

Detection windows for commonly abused drugs

Drug		Detection window
Cocaine		1 to 4 days
Amphetamines (amphetamine, methamphetamine, MDMA)		1 to 4 days
Opioids (heroin, codeine, morphine, hydrocodone, oxycodone)		1 to 4 days
Fentanyl/norfentanyl		1 to 4 days
Benzodiazepines (alprazolam, diazepam, lorazepam)		1 to 10 days
Burprenorpine, norbuprenorphine		1 to 10 days
Barbiturates	Short-acting (pentobarbital, secobarbital)	1 to 3 days
	Long-acting (phenobarbital)	1 to 30 days
Marijuana	Acute use	1 to 5 days
	Chronic exposure	1 to 30 days

MDMA: 3,4-methylenedioxymethamphetamine

Table 2

Cross-reactivity that can lead to a false-positive result

Drug tested	Common drugs with cross-reactivity
Amphetamines	Atenolol, bupropion, ephedrine, labetalol, propranolol, pseudoephedrine, ranitidine, trazodone
Barbiturates	Ibuprofen, naproxen, phenytoin
Benzodiazepines	Oxaprozin, sertraline
Cannabinoids	Efavirenz, ibuprofen, naproxen, pantoprazole
LSD	Amitriptyline, bupropion, buspirone, fentanyl, fluoxetine, haloperidol, imipramine, labetalol, metoclopramide, risperidone, sertraline, trazodone, verapamil
Opioids	Amisulpride, fluoroquinolones, quetiapine, rifampicin, tramadol, verapamil
Oxycodone	Codeine, hydrocodone, hydromorphone
Phencyclidine	Lamotrigine, tramadol, venlafaxine
Tricyclic antidepressants	Quetiapine

Clinical Point

GC-MS confirms drug use more definitively than EIA, but it rarely is used in clinical settings because it is time-consuming and expensive

Discuss this article at www.facebook.com/CurrentPsychiatry

• **In vitro adulterants** are substances added to urine samples after urination to avoid drug detection. Active ingredients include glutaraldehyde (Clean-X), sodium or potassium nitrate (Klear, Whizzies), pyridinium chlorochromate (Urine Luck), andj (Stealth).[9]

• **Other methods** used to avoid drug detection include substituting a urine sample with someone else's clean urine or adding household products, such as bleach, vinegar, or pipe cleaner.

You can spot and prevent false-negatives by:

Directly observing the patient, which helps to prevent individuals from adding foreign materials or substituting the urine sample.

Visually inspecting the urine helps identify sample tampering. Adding household adulterants can produce unusually bubbly, cloudy, clear, or dark sample.

On-site analyses and laboratory analyses of samples. Commercially sold kits can detect adulterants by on-site analysis, such as Intect 7 and AdultaCheck 4 test strips.[9] Simple on-site methods can help discover

tampering, such as measuring the urine's temperature and using pigmented toilet water. The U.S. Substance Abuse and Mental Health Services Administration recommends validity checks during laboratory analysis for all urine samples, including temperature, creatinine, specific gravity, pH, and tests for oxidizing adulterants.[10]

Considerations

The results of UDS should not be interpreted as absolute. Knowing the sensitivity and specificity of the UDS that your institution uses and the patient's current medication regimen is valuable in distinguishing between true results and false-positives. False-positives can strain the relationship between patient and provider, thus compromising care. When EIA is positive and patient denies substance use, confirming the result with GC-MS may be a good clinical practice.[3] Ordering a GC-MS test can be helpful in situations requiring greater precision, such as in methadone or pain management clinics, to verify if the patient is taking a prescribed medication properly or to rule out illicit exposures with greater certainty.

References

1. Substance Abuse and Mental Health Services Administration. Results from the National Survey on Drug Use and Health: detailed tables. Prevalence estimates, standard errors, *P* values, and sample sizes. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf. Published September 8, 2016. Accessed February 7, 2017.
2. Schweitzer BN. An assessment of lateral flow immunoassay testing and gas chromatography mass spectrometry as methods for the detection of five drugs of abuse in forensic bloodstains. https://open.bu.edu/bitstream/handle/2144/19477/Schweitzer_bu_0017N_12357.pdf?sequence=1. Published 2016. Accessed February 7, 2017.
3. Pawlowski J, Ellingrod VL. Urine drug screens: when might a test result be false-positive? Current Psychiatry. 2015;14(10):17,22-24.
4. Tenore PL. Advanced urine toxicology testing. J Addict Dis. 2010;29(4):436-448.
5. AIT Laboratories. Physician's reference for urine and blood drug testing and interpretation. http://web.archive.org/web/20160312195526/http://aitlabs.com/uploadedfiles/services/pocket_guide_smr086.pdf. Published 2011. Accessed February 7, 2017.
6. Saitman A, Park HD, Fitzgerald RL. False-positive interferences of common urine drug screen immunoassays: a review. J Anal Toxicol. 2014;38(7):387-396.
7. Namera A, Kawamura M, Nakamoto A, et al. Comprehensive review of the detection methods for synthetic cannabinoids and cathinones. Forensic Toxicol. 2015;33(2):175-194.
8. Cone EJ, Lange R, Darwin WD. In vivo adulteration: excess fluid ingestion causes false-negative marijuana and cocaine urine test results. J Anal Toxicol. 1998;22(6):460-473.
9. Jaffee WB, Trucco E, Levy S, et al. Is this urine really negative? A systematic review of tampering methods in urine drug screening and testing. J Subst Abuse Treat. 2007;33(1):33-42.
10. Substance Abuse and Mental Health Services Administration. Mandatory guidelines for federal workplace drug testing programs. Federal Register. 2004;69:19644-19673.

Acknowledgment

The authors would like to thank Steven Lippmann, MD, for his mentorship, encouragement, and editorial support.

Clinical Point

A validity check is recommended for all urine samples, including temperature, creatine, specific gravity, pH, and adulterants