THE CARLAT REPORT
ADDICTION TREATMENT

A CE/CME Publication

CURRENT COVERAGE OF TOPICS IN ADDICTION MEDICINE

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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Laboratory Testing

Learning Objectives
After reading these articles, you should be able to:

1. Interpret both presumptive and confirmatory urine toxicology results.
2. Identify which labs to order for patients with substance use disorders and how to interpret the results.
3. Summarize some of the findings in the literature regarding addiction treatment.

Urine Drug Screens: What You Need to Know

Brooke Lifland, MD. Resident in psychiatry, Yale University. New Haven, CT.

Dr. Lifland has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Highlights From This Issue

- Urine toxicology is an important tool but can be tricky to use properly. We review what you need to know.
- Dr. Will Becker tells us how best to incorporate toxicology testing in clinical practice.
- We discuss the latest data on buprenorphine and methadone for the treatment of OUD.

What should you do with unexpected urine toxicology results? When should you suspect a false test? What is confirmatory testing? In this article, we'll answer these questions and more, giving you everything you need to know about urine toxicology testing in the clinical setting.

The tests: Screening and confirmation
There are two types of urine toxicology testing—presumptive testing, commonly called a urine drug screen (UDS), and confirmatory testing, which is used to verify UDS results. Both tests detect metabolites excreted into the urine after substance use.

UDS uses a technology called *immunoassay*, which relies on antibody binding (Melanson SEF, *Clin Lab Med* 2012;32(3):429–447). It's quick (a day or two at an outside laboratory or a few hours in house) and inexpensive (<$30), but can be prone to false results.

Confirmatory testing, though highly accurate, is slower (72 hours or more)

Continued on page 4

Q&A With the Expert

Lab Testing for Patients With Substance Use Disorders

Will Becker, MD

Associate Professor, Yale University. Medical director, Opioid Reassessment Clinic, VA Connecticut Healthcare System. New Haven, CT.

Dr. Becker has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CATR: Can you tell us a little about yourself?
Dr. Becker: I'm a general internist with a specialty in addiction medicine and pain management. I spend my time doing clinical research and directing a pain clinic for patients with opioid misuse and opioid use disorder (OUD).
CATR: What labs do you order for a new patient?
Dr. Becker: To start, I always check what lab values are already available, usually through their primary care provider. But let's assume that I don't have any labs for this patient. In the setting of an addiction clinic, I would like a complete metabolic panel, liver function tests, a complete blood count, and a screening urine toxicology or urine drug screen (UDS) that includes fentanyl and buprenorphine. And I also screen for viral hepatitis—hepatitis A, B, and C.
CATR: What might drive you to order additional labs?
Dr. Becker: If I know that the patient has a history of

Continued on page 2

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Expert Interview

Continued from page 1

incarceration, then I will want to screen for latent tuberculosis (TB). A latent TB infection comes about when someone has been infected with TB mycobacteria, but their immune system has largely neutralized the infection. They don't have any symptoms, but there is a small amount of live mycobacteria lurking in their body that could reactivate later.

CATR: There are several ways to test for latent TB. How do you sort through them?

Dr. Becker: The most widely used is the skin antigen test, which is the cheapest test and is easy to use. You'll hear several names used for it interchangeably, like tuberculin skin test (TST), Mantoux, or purified protein derivative (PPD). It's a small intradermal injection, and swelling at the site 48–72 hours later indicates a positive test. The drawback is that the patient needs to see a provider in a couple of days to read it. If I worry the patient might not come back, I order a blood test: a QuantiFERON or T-Spot. Any positive result on the screening triggers a chest x-ray to exclude the possibility of active TB.

CATR: Do you recommend any other testing based on the patient's history?

Dr. Becker: Checking for sexually transmissible infections is important if the patient has a history of high-risk sexual activity. I always order HIV screening and test for syphilis with a rapid plasma reagin (RPR) in these patients.

CATR: Of all the labs that we've covered so far, which ones do you follow sequentially?

Dr. Becker: If I know that a patient is continuing to engage in high-risk sexual activity or intravenous drug use, I will repeat the viral hepatitis panel, HIV, and RPR screening annually. But otherwise, once I have that baseline set we've discussed, as an addiction provider, the only lab that I consistently follow over time is the UDS, assuming that the patient is seeing a primary care provider.

CATR: Let's talk more about UDS. How do you introduce this topic to patients?

Dr. Becker: I begin by explaining the rationale for testing as plainly as possible, trying to frame it as part of collaborative care. I might say, "We'd like to work with you to help you manage your disease of addiction and improve your overall function. Part of that is using the UDS as a tool. It helps us know how our treatments are working and helps keep you safe." A useful analogy is routine international normalized ratio (INR) tests for patients on warfarin or glucose monitoring for diabetes; the results of the test will tell you whether the treatment is working. I try to preempt any objections up front by saying, "It's not about catching you, judging you, or getting you in trouble. It tells us when we need to offer you more support." We want to emphasize the message: "This is a tool we use to help you recover."

CATR: Do patients ever disagree with the UDS requirement?

Dr. Becker: Sometimes. In a pain management clinic, patients may deny that they have an addiction at all (and indeed they may not). The mindset is, "Why do I need to prove myself if I don't have anything wrong with me?" Other patients might be afraid of how we'll use the test results. Some patients are scared of embarrassment if the UDS reveals they are continuing to use substances. Ultimately, we require it, but understanding why a patient might resist can help us keep the conversation friendly. Our goal is to remain collaborative; having a patient drop out of treatment because we require regular UDS would be a terrible outcome. But it seems to me that most patients are aware of the need for UDS. And even if there is some resistance up front, that tends to quickly dissipate. The goal is to make the UDS a matter-of-fact, routine part of the clinic visit.

CATR: You mentioned some patients see the UDS as punitive, a way for providers to "catch" them using drugs. Do some providers treat it that way?

Dr. Becker: Yes, and I ask those providers to think about the role of stigma and how we risk driving patients who are already so stigmatized away from treatment. Even the language used around drug testing is laden with stigma. For example, we talk about UDS as being "clean" or "dirty," as if using drugs somehow makes one dirty. We should stick to medical terms: A UDS is either "negative" or "positive." And "positive" can be broken down further into "appropriate for prescription" if the urine shows something that is prescribed, or "inappropriate for prescription" if the urine indicates nonprescription substance use.

CATR: How often do you order UDS? Every visit, randomly, at regular intervals?

Dr. Becker: That's an interesting question, and I would have given you a different answer before COVID-19. For patients with OUD, prior to COVID-19, we ordered a UDS at every visit early on in treatment and then spaced them out as

Continued on page 3

Expert Interview

Continued from page 2

the patient achieved stability. At the time, that seemed like an ideal arrangement—the caveat, of course, is that the facility I was working in had the resources to do that. But COVID-19 significantly disrupted that schedule due to the challenges of getting tests done. It forced us to rethink our strategy. We didn't do any UDS at all during the lockdown in April 2020, since our visits were entirely virtual. But now, even though patients can come in, we have been doing UDS less frequently. Performing a UDS at every visit seemed burdensome to the patient and it rarely changed management.

CATR: So what is your updated strategy?

Dr. Becker: Overall, it's similar to before, but much less rigid. We always get a UDS at baseline, and a couple more early on in treatment, but then pretty quickly spread them out to monthly and then every three months. For our very stable patients, we do it as seldom as every six or even every 12 months.

CATR: Have you seen a change in outcomes as you've spaced out UDS?

Dr. Becker: Not really. Of course, along with COVID-19, another huge, relatively recent issue is fentanyl. We know that fentanyl is contaminating many illicit drugs, so it is frequently being used inadvertently. And it has such an elevated overdose risk that we really want to know if a patient is being exposed to it without their knowledge. So fentanyl is a force that drives us toward getting UDS. Honestly, I sometimes wonder whether we'd be doing UDS at all if it weren't for fentanyl contaminating the drug supply.

CATR: How do you handle a UDS result that differs from the patient's report?

Dr. Becker: In my experience, getting into the whole "Why were you not truthful?" approach tends to go nowhere, so I try very hard not to get into an argument. I simply say, "Well, it looks like you did have use of X substance" and just assert it as fact. Again, couching it in terms of safety is a good strategy. I don't waste time with saying, "This is disappointing because you told me one thing and we're seeing something else." Part of the disease of addiction, for some people, can be non-truthfulness. So I quickly state the fact of the test result, then pivot to problem-solving: "How should we work together to address this? How are we going to help you given the result of this test?"

> **"We know that fentanyl is contaminating many illicit drugs, so it is frequently being used inadvertently. And it has such an elevated overdose risk that we really want to know if a patient is being exposed to it without their knowledge. So fentanyl is a force that drives us toward getting UDS."**
>
> Will Becker, MD

CATR: What about the patient who tries to explain a positive UDS as secondhand exposure? Is there any truth there?

Dr. Becker: I'm thinking of the colloquial term "hot boxing," when people smoke marijuana in a closed car and there's enough smoke in the air for everyone to get intoxicated. I've heard this explanation from patients regarding smoked substances like cannabis and crack cocaine. But if a drug reaches a high enough serum level so that enough is excreted into the urine and detected on UDS, the patient has essentially used the drug. There isn't a big distinction whether they were the one smoking it or not.

CATR: How do you proceed in this situation?

Dr. Becker: I return to the principle of using UDS as a tool of safety and recovery. So, if the patient says, "I wasn't intending to use," my response is matter-of-fact: "Well, that's the result you got. If your intention is not to use, let's work on avoiding situations where you get passively exposed to so much smoke."

CATR: And what about poppy seeds causing a false positive opioid result?

Dr. Becker: You know, I've seen it. You do have to eat a lot of poppy seeds, but it can happen. The patient I'm convinced this happened with was eating a good-sized poppy seed bagel or two every day. He stopped eating the bagels and the positive opiate result disappeared.

CATR: Can you explain this process a bit? Did you do confirmatory testing?

Dr. Becker: We did, although in the case of poppy seeds, the confirmatory testing is not always all that helpful. The screening UDS can give unexpected or false results from time to time, while confirmatory testing is highly sensitive and specific.

CATR: You said confirmatory testing might not be helpful to differentiate poppy seeds from opioids. Why is that?

Dr. Becker: Well, it might be helpful, but it won't be definitive. To explain that, you have to know a bit about opiate metabolism. Natural opiates are derived from poppy seeds, so we would expect to see natural opiate metabolites on the gas chromatography–mass spectrometry (GC-MS) results of someone eating lots of poppy seeds. There shouldn't be any cross-reactivity with semi-synthetic or synthetic opioids like oxycodone, buprenorphine, or fentanyl. The metabolites you would see on GC-MS are morphine and possibly codeine.

CATR: So, how do you differentiate heroin from eating poppy seeds? Heroin also is metabolized to morphine.

Dr. Becker: Yes, that is true. The difference is that there is an intermediate product between heroin and morphine that is outside the metabolic pathway of any other opioids, including poppy seeds. It is called 6-monoacetylmorphine, usually abbreviated as 6-MAM. Finding 6-MAM in urine is definitive for heroin use, but its half-life is short and it is only detectable within one day of heroin use (Cone EJ et al, *J Anal Toxicol* 1991;15(1):1–7). 6-MAM used to be a very useful clinical marker, but its utility is declining now that fentanyl is so prominent.

CATR: Prescription and over-the-counter medications can cause false positives on a UDS as well.

Dr. Becker: Absolutely. In fact, we see false positives from other medications more commonly than from poppy seeds. It's important for clinicians to familiarize themselves with common false positive culprits. *(Editor's note: See the page 1 article for more details on UDS and confirmatory testing)*

CATR: Thank you for your time, Dr. Becker.

Urine Drug Screens: What You Need to Know

Continued from page 1

and more expensive (up to $250); therefore it is reserved for verifying questionable UDS results. It works by volatilizing metabolites, then using gas chromatography–mass spectrometry to determine their chemical composition (Wu A et al, *Clin Toxicol (Phila)* 2012;50(8):733–742). Some laboratories automatically do confirmatory testing on all positive UDS results (a practice known as reflex testing), while others don't. If you want a negative result confirmed to ensure that a patient is taking something you prescribed, you will almost always need to order the confirmatory test separately. Keep in mind that labs discard urine samples after a set time, so familiarize yourself with institutional protocols and be aware of how long you have to order confirmatory testing.

Timing is everything

The results of a urine test depend substantially on its timing. Some substances (cocaine, short-acting opioids) create metabolites that are only excreted for a short amount of time, while others (cannabis, fentanyl) create metabolites that are detectable for as long as a month. Metabolites can be found in urine for varying lengths of time based on a host of factors: individual metabolism, fat solubility, short-acting vs long-acting formulations, frequency of use, and comorbidities such as kidney or liver disease. The times listed in the "Overview of UDS Results" table can be useful when interpreting UDS results and deciding whether to order confirmatory testing. For example, a patient could have a positive UDS for cannabis even after abstaining from use for a month, whereas that is not the case for a substance like cocaine.

Urine drug screen results

Immunoassay results are reported as "positive" or "negative" based on a predetermined cutoff. Sensitivity and specificity values vary according to the drug being detected and the test manufacturer, but they are generally reliable. Unfortunately, UDS results can occasionally present problems.

Overview of UDS Results

Substance (Time Detectable in Urine)	Potential Agents Causing False Positive Results		Potential Agents Causing False Negative Results
Alcohol (ethyl glucuronide) (2–3 d)	Short-chain alcohols (isopropyl), urinary tract infection		Urinary tract infection
Amphetamine (48 h) Methamphetamine (48 h)	Amantadine Bupropion Chlorpromazine Desipramine Dextroamphetamine Labetalol Levomethamphetamine Methylphenidate	Phentermine Phenylephrine Promethazine Pseudoephedrine Ranitidine Selegiline Thioridazine Trazodone	MDMA
Barbiturates Short-acting (24 h) Long-acting (3 w)	—		—
Benzodiazepines Alprazolam (3–5 d) Lorazepam (3–5 d) Diazepam (30 d) Clonazepam (30 d)	Oxaprozin (NSAID) Sertraline		Benzos without oxazepam or nordiazepam metabolite, such as alprazolam or lorazepam
Cannabis Single use (3 d) Four times/week (5–7 d) Daily use (10–15 d) Long-term daily use (>30 d)	Dronabinol Efavirenz NSAIDs Proton pump inhibitors		Synthetic cannabinoids (K2, spice)
Cocaine (4 d)	—		—
Opioids Codeine (48 h) Fentanyl (7–26 d) Heroin (8 h) Hydromorphone (2–4 d) Methadone (3 d) Morphine (2–3 d) Oxycodone (2–4 d)	Dextromethorphan Diphenhydramine Poppy seeds Quetiapine Quinolones	Rifampin Risperidone Trazodone Verapamil	Synthetic opioids such as methadone, oxycodone, fentanyl, and tramadol (separate immunoassays are required)
Phencyclidine (8 d)	Alprazolam Clonazepam Dextromethorphan Diphenhydramine Doxylamine Ibuprofen	Imipramine Ketamine Meperidine Thioridazine Tramadol Venlafaxine	—

False positives

False positives occur when antibodies meant to bind to a specific drug metabolite cross-react with another similarly structured molecule. Some immunoassays are more prone to false positives than others. The table presents a fairly comprehensive list of common false positives.

False negatives

False negatives occur for several reasons. Sometimes, the UDS itself is not designed to detect the metabolites of the substance you are looking for. Benzodiazepines are a well-known example. UDS detects nordiazepam and/or oxazepam, which are metabolites of some but not all benzodiazepines (see "Benzodiazepine Metabolic Pathway" figure on page 5). If your patient is taking alprazolam, lorazepam, or clonazepam, which do not produce these metabolites, the immunoassay can show a false negative benzodiazepine result. Of course, these are some of the most commonly misused benzodiazepines. In such a situation, you can order confirmatory testing that looks for metabolites of these drugs.

Continued on page 5

Urine Drug Screens: What You Need to Know

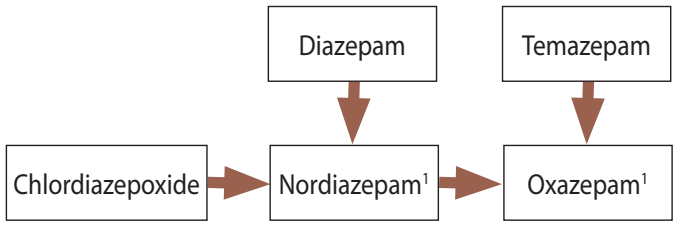
Continued from page 4

False negatives can also result when a patient is using opioids. UDS reliably detects metabolites of naturally derived opiates such as morphine, codeine, and heroin. Semi-synthetic and synthetic opioids (such as buprenorphine, methadone, hydrocodone, oxycodone, tramadol, and fentanyl) bind erratically and only sometimes result in a positive test. Therefore, if your institution does not have an automatic UDS for semi-synthetic and synthetic opioids, you will need to order individual screens for them (Milone MC, *J Med Toxicol* 2012; 8(4):408–416). See "Opioid Metabolic Pathway" figure.

Lastly, improper antibody binding can result in a false negative, which can happen if a patient intentionally adulterates their urine sample. Several commercially available adulterants and household products can be used to produce negative results. If you are suspicious, consider direct observation and order a urinalysis along with the UDS. Specific gravity or pH values outside the normal range can suggest that a sample has been tampered with. Some labs test to determine whether a sample is valid by looking for the presence of bleach, glutaraldehyde, and chlorochromates (which are not normally present) as well as creatinine, nitrites, and uric acid (which should be present but are often absent from faked samples). Keep in mind that even direct observation and lab results can be circumvented if the patient substitutes fake urine and uses a prosthesis such as the "Whizzinator." A quick temperature check can uncover at least some of these attempts at deception.

Benzodiazepine Metabolic Pathway

Note that common benzodiazepines such as lorazepam, clonazepam, and alprazolam are not included.

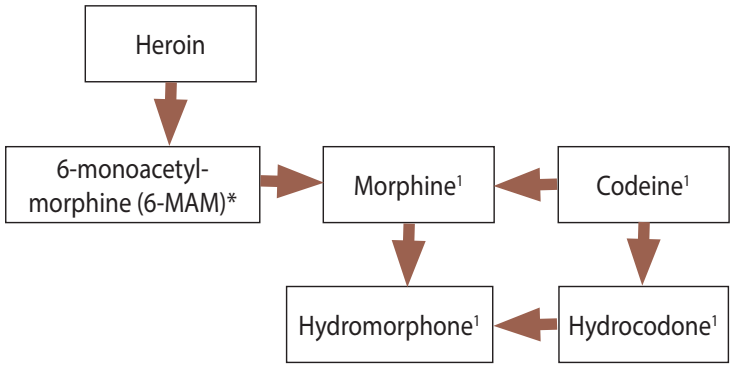


[1]tested for as part of UDS

Adapted from: Craven CM et al, Practical Pain Management 2014;14(1).

Opioid Metabolic Pathway

Note that synthetic opioids such as oxycodone, methadone, and buprenorphine are not included.



[1]tested for as part of UDS

Adapted from: Reisfield GM et al, Ann Clin Lab Science 2007;37(4):301–314.

Opioid Metabolites Detectable by Urine Confirmation

Drug \ Metabolite	6-MAM	Codeine	Morphine	Hydromorphone	Hydrocodone
Codeine	–	+	+	+	+
Heroin	+	–	+	+	–
Hydrocodone (Vicodin)	–	–	–	+	+
Hydromorphone (Dilaudid)	–	–	–	+	–
Morphine	–	–	+	+	–

Drug \ Metabolite	Buprenorphine	Norbuprenorphine
Buprenorphine	+	+

Drug \ Metabolite	Fentanyl	Norfentanyl
Fentanyl	+	+

Drug \ Metabolite	Oxycodone	Oxymorphone
Oxycodone	+	+
Oxymorphone (Opana, off the market)	–	+

Confirmatory testing

Confirmatory testing is reported differently than a qualitative UDS report.

Continued on page 7

Research Updates

ALCOHOL

Treating Agitation in ICU Patients With Alcohol Use Disorder?

Jedidiah Perdue, MD. Dr. Perdue has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Vourc'h M et al, *JAMA* 2021;325(8):732–741

STUDY TYPE: Randomized clinical trial

It's known that people who drink unhealthy amounts of alcohol are more likely to get agitated if they're admitted to the ICU. What to do about it is less well understood. In this study, researchers reasoned that mimicking some of alcohol's effects with the GABA-B agonist baclofen might decrease agitation in patients on mechanical ventilation. The strategy makes sense pharmacologically, and baclofen even has some evidence for treating alcohol use disorder (see *CATR,* May/Jun 2020), but the results here were short of a slam dunk.

This double-blind, randomized study involving 314 patients was conducted across 18 medical and surgical ICUs. Eligible patients were those with unhealthy alcohol use (greater than seven weekly standard drinks for women, greater than 14 for men) expected to require 24 hours or more of mechanical ventilation. Patients were randomized to placebo or baclofen, which was dosed based on eGFR and added to a standard anesthetic cocktail to maintain light sedation. The amount of baclofen used was quite high: 50–150 mg daily. For context, the FDA's maximum recommended dose of baclofen is 80 mg daily. Unfortunately, the investigators did not lay out their rationale for choosing such a high dose.

This study's primary outcome was one or more agitation-related events, such as self-extubation, pulling out lines, leaving against medical advice, and aggression. Researchers also examined a host of secondary outcomes that included 28-day mortality, oversedation, length of stay, and duration of intubation, among others.

Compared to placebo, patients receiving baclofen were significantly less likely to have an agitation-related event (29.7% vs 19.7%). However, the baclofen group had significantly longer ICU stays (14 vs 11 days), spent more time in deep sedation (7.0 vs 4.6 days), and had fewer vent-free days (14 days vs 19) than placebo. Mortality and other secondary outcomes were similar between the groups.

This study had several notable limitations. First, it lacked a validated method of quantifying alcohol intake other than self-report. We simply don't know how much alcohol patients drank. Another limitation, probably more significant, was the lack of a delirium assessment. Other GABAergic medications, such as benzodiazepines, are associated with delirium, so baclofen could plausibly have increased rates of delirium in these patients as well—however, we don't know if that occurred in this study. Alcohol withdrawal delirium (AWD) can be a source of agitation in itself and is treated by GABAergic medications, so it is not clear whether baclofen was treating AWD or agitation-related events stemming from some other etiology.

CARLAT TAKE

Baclofen, at high doses, may modestly reduce agitation among ventilated patients with unhealthy alcohol use but at the cost of longer ICU stays and more time on mechanical ventilation. At this point, we would not recommend using high doses of baclofen prophylactically to prevent agitation in the ICU.

OPIOIDS

Opioid Agonist Treatment and Decreased Mortality

David Moltz, MD. Dr. Moltz has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

REVIEW OF: Santo T et al, *JAMA Psychiatry* 2021;78(9):979–993

STUDY TYPE: Systematic review and meta-analysis

It has been well established that opioid agonist treatment (OAT) saves lives by reducing rates of fatal drug overdose. But OAT can reduce mortality in other ways as well. In this study, researchers analyzed 15 randomized clinical trials and 36 cohort studies across nearly 750,000 participants in order to conduct the first systematic examination of the association of OAT with various causes of death among patients with opioid use disorder.

As expected, the authors found that OAT (methadone or buprenorphine) was associated with an impressive reduction in all-cause mortality; patients receiving OAT died less than half as often as those not receiving OAT (RR 0.47). Importantly, this risk reduction was the same whether patients were taking methadone or buprenorphine and was remarkably consistent across a host of patient characteristics including age, gender, HIV or hepatitis C viral status, and whether the patient used drugs intravenously. Researchers found that patients receiving OAT had decreased mortality due to several specific causes of death as well. Not only did they have a two-thirds reduced risk of unintentional drug overdose (RR 0.35), but they also had reduced risks of death due to suicide (RR 0.48), cancer (RR 0.72), alcohol (RR 0.59), and cardiovascular conditions (RR 0.69).

The six studies specifically looking at OAT outcomes in and around incarceration were particularly striking. The single study of OAT during incarceration showed large decreases in the risk of all-cause mortality (RR 0.24) and deaths related to drugs or suicide (RR 0.17). Similarly, five studies showed dramatic reductions in risk from all-cause mortality (RR 0.24) and drug-related deaths (RR 0.19) in the month after release for those who received OAT compared to those who didn't.

Researchers found two caveats that providers should be aware of, though neither was unexpected. First, and most obviously, OAT must be taken to be effective. Patients became

Continued on page 8

CE/CME Post-Test

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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

1. Which of the following benzodiazepines is consistently detected on a routine urine drug screen (UDS) (LO #1)?
   [ ] a. Lorazepam
   [ ] b. Alprazolam
   [ ] c. Diazepam
   [ ] d. Clonazepam

2. According to Dr. Becker, how does confirmatory testing compare to UDS (LO #2)?
   [ ] a. It is not as sensitive or specific as UDS
   [ ] b. It is highly sensitive and specific compared to UDS
   [ ] c. It is more sensitive but less specific than UDS
   [ ] d. It is more specific but less sensitive than UDS

3. According to a recent systematic review and meta-analysis of opioid agonist treatment (OAT), patients receiving OAT were _____ as likely to die from all-cause mortality compared to those not receiving treatment (LO #3).
   [ ] a. About a quarter [ ] b. Less than half [ ] c. Two-thirds [ ] d. Four-fifths

4. Semi-synthetic and synthetic opioids can produce inconsistent results on routine UDS (LO #1).
   [ ] a. True [ ] b. False

5. You perform baseline labs for your patient with substance use disorder at their first visit. The patient does not use drugs intravenously or engage in high-risk sexual activity, and they see their primary care physician regularly. Over subsequent visits with your patient, which lab test(s) does Dr. Becker recommend you follow sequentially (LO #2)?
   [ ] a. HIV and RPR screens [ ] b. LFTs [ ] c. UDS [ ] d. Confirmatory tests

Urine Drug Screens: What You Need to Know

Continued from page 5

Rather than reporting a positive or negative, confirmatory testing reports the presence and concentration of individual metabolites. Although these reports contain a lot of potentially useful information, they can be challenging to interpret and require knowledge of relevant metabolic pathways.

For example, a confirmatory test for diazepam would show the presence of nordiazepam and oxazepam, whereas a confirmatory test for temazepam would only report the presence of oxazepam (refer to the "Benzodiazepine Metabolic Pathway" figure). The confirmatory test for a patient taking oxazepam would, likewise, only show oxazepam. Benzodiazepines outside of this pathway, such as clonazepam or alprazolam, have their own metabolites to test for. When examining the test results, look for a key that tells you which metabolites correspond to which substances. When in doubt, call the laboratory for clarification. See the interview with Dr. Becker in this issue for another example of using metabolic pathways to interpret confirmatory testing, this time with opioids.

In general, unlike electrolyte or cell count values, the concentration of a metabolite at a single point in time is not particularly useful. Trending values over time, however, can help determine whether a patient has returned to use. Metabolite concentrations that consistently fall from one appointment to another can indicate that the patient is abstaining. Conversely, a large spike in metabolite concentration suggests recent use. While useful, trending isn't bulletproof; dehydration and P450 inhibition can lead to higher-than-expected levels, giving a false impression of increased or sustained use (Kapur B and Aleksa K, *Crit Rev Clin Lab Sci* 2020;57(8):548–585).

CARLAT VERDICT: UDS deserves its role as a clinic workhorse but can be prone to false positives and negatives. If you encounter an unexpected positive result, look for agents known to cause false positives. If you encounter an unexpected negative result, double-check that the assay tests for the substance you are looking for, clarify the timeline, and consider the possibility of sample tampering. If doubt remains, order confirmatory testing.

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This Issue:
Laboratory Testing
May/June 2022

Next Issue:
Addiction and Personality Disorders
July/August 2022

Research Updates

Continued from page 6

particularly vulnerable if they discontinued treatment, with all-cause mortality increasing six-fold in the first month (RR 6.01) and remaining nearly doubled (RR 1.81) for as long as they were not receiving OAT. In addition, mortality was twice as high during the first month of methadone treatment (RR 2.01) compared to the rest of the time on OAT. This is likely because methadone doses are titrated gradually, thus potentially leaving patients vulnerable while still on a low dose. Buprenorphine can be titrated much more quickly, which is likely why this trend was not observed among those receiving buprenorphine.

CARLAT TAKE

OAT is a powerful tool for reducing death due to a variety of causes, both related and unrelated to drugs. This trend is consistent across demographic groups and is especially pronounced during and upon release from incarceration. Mortality increases when OAT is discontinued, particularly in the first month.

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