THE CARLAT REPORT
ADDICTION TREATMENT

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CURRENT COVERAGE OF TOPICS IN ADDICTION MEDICINE

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Learning Objectives

After reading these articles, you should be able to:

1. Assess and treat patients withdrawing from multiple substances simultaneously.
2. Develop pharmacologic and nonpharmacologic treatment strategies for managing cannabis withdrawal.
3. Identify the physiological mechanisms underlying withdrawal syndromes and their expected time course.
4. Summarize some of the findings in the literature regarding addiction treatment.

Effective Management of Buprenorphine-Precipitated Opioid Withdrawal

Jaewon Lee, MD, MPH. PGY-2, psychiatry resident, University of Rochester Medical Center, Rochester, NY.

Dr. Lee has no financial relationships with companies related to this material.

Buprenorphine is an effective first-line treatment of opioid use disorder (OUD), but because it is a partial opioid agonist, starting buprenorphine (a process known as induction) can lead to precipitated withdrawal in patients with residual opioid agonist in their system. Carefully following induction procedures can minimize this risk, but precipitated withdrawal is always a possibility. In this article, we'll review buprenorphine induction procedures that minimize the risk of withdrawal and discuss how to manage withdrawal if it occurs.

Avoiding withdrawal

The standard induction procedure involves two steps. The first step is to quantify opioid withdrawal symptom

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Highlights From This Issue

Feature Q&A
Substance use disorders are highly comorbid, and patients commonly have to be treated for multiple withdrawals simultaneously.

Q&A on page 6
Cannabis withdrawal is prevalent among people who regularly use cannabis and can interfere with patients' ability to abstain from use, though it is generally underrecognized.

Article on page 8
The symptoms and time course of withdrawal syndromes depend on the pharmacology of the drug that the patient is withdrawing from, namely its mechanism of action and half-life.

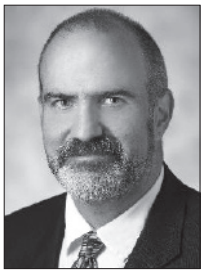
Q&A With the Expert

Managing Withdrawal From Multiple Substances

Darius Rastegar, MD

Associate professor of medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Dr. Rastegar has no financial relationships with companies related to this material.



CATR: Please introduce yourself.

Dr. Rastegar: I'm an internist by training, practicing in addiction medicine for about 30 years. I am at Johns Hopkins Bayview Medical Center, where I provide primary care with a focus on people with substance use disorders (SUDs), and I am the medical director for our inpatient withdrawal management unit. I'm also the program director for the addiction medicine fellowship.

CATR: How common is it for patients to have multiple SUDs?

Dr. Rastegar: I would say it's more the rule than the exception. Most people that we see are using multiple substances, and if you include nicotine, it's almost a universal phenomenon. Most concerning is the use of opioids in combination with other central nervous system (CNS) depressants because of the high risk of mortality. Alcohol and other sedatives are also concerning because of the risk of medication complications during withdrawal. And these

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are drugs that we tend to focus on when managing withdrawal medically: alcohol, sedatives, and opioids.

CATR: Do certain substances tend to cluster together?

Dr. Rastegar: To my knowledge, there aren't any definitive data on that front, but we do see patterns. For example, stimulant use commonly goes along with alcohol or opioids. And I've found that it's uncommon to see patients who are misusing sedatives alone—almost all of them are also using opioids or some other drug. On the flip side, there are many people who use alcohol or opioids pretty much exclusively.

CATR: What are some challenges in assessing patients who are using multiple substances?

Dr. Rastegar: The challenges aren't all that different from patients who use a single substance. You should stick to the basic principle of starting with a thorough patient interview, getting a good history, and finding out what they've been using. In most circumstances, you'll be treating patients who are voluntarily seeking care, so I've found they are generally forthcoming. But there are challenging situations that can make history-gathering tough. Sometimes patients may not disclose which substances they have been using because of stigma or potential legal consequences. Other times, patients may be intoxicated, which makes it difficult to gather a good history. And especially during withdrawal, patients can be irritable and uncooperative. Withdrawal is uncomfortable, and these are not very happy patients.

CATR: And how do you handle these situations?

Dr. Rastegar: An open, accepting approach can be helpful. Reassure the patient that we are here to help. And we can get information through laboratory testing—an alcohol level through breath or serum can tell us if the patient has been drinking recently. A urine drug screen will tell us about use of some other substances. If they are intoxicated, wait until their alcohol level comes down. If they are irritable due to being in withdrawal, starting with empiric treatment can make them much more comfortable.

CATR: Patients withdrawing from more than one substance may experience multiple withdrawal syndromes simultaneously. That can be challenging to assess because many of the symptoms overlap. How do you sort through all that?

Dr. Rastegar: It's true that some withdrawal symptoms are not all that specific. You can't always say, "This symptom is due to withdrawal from alcohol and this other symptom is due to withdrawal from opioids" when the patient has been using both substances—it doesn't usually work like that. Irritability is probably a universal symptom during withdrawal, regardless of substance. Diaphoresis, anxiety, and restlessness are seen with both alcohol and opioid withdrawal, while we typically think of tremors as only accompanying alcohol or sedative withdrawal. Piloerection and dilated pupils are pretty specific to opioid withdrawal, though they may not be present. And of course, we think of gastrointestinal complaints with opioid withdrawal, but those can come with alcohol as well.

CATR: How do you treat patients who are presenting with overlapping withdrawal syndromes?

Dr. Rastegar: The general approach is to treat both withdrawal syndromes independently. You shouldn't substantially change your clinical approach to treating alcohol withdrawal just because the patient is also withdrawing from opioids. Alcohol withdrawal is more likely to lead to serious complications, so I would prioritize that.

CATR: Tell us about your approach to opioid withdrawal.

Dr. Rastegar: Withdrawal management alone for opioid use disorder (OUD) is not adequate treatment. The standard of care is to start a medication for OUD (MOUD), either buprenorphine or methadone. Many have had experience with one or both medications and have a preference. If they want methadone, you can start them on methadone 30 mg and titrate up. The trick with methadone is ensuring that patients have follow-up in a federally recognized opioid treatment program (OTP), aka a "methadone clinic." Federal regulations limit methadone prescribing to three days; after that, patients need to be part of a methadone

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prescribing program. A preference for buprenorphine can be a little more complicated because of the risk of precipitated withdrawal during initiation. There are a few approaches to starting buprenorphine (*Editor's note: See "Three Buprenorphine Dosing Strategies When Transitioning From Other Opioids" in* CATR *Apr/May/Jun 2024*). In my personal practice, which is in an inpatient setting, I sometimes give 30 mg of methadone up front if the patient is in severe withdrawal, just to stabilize them, and then use a low-dose initiation of buprenorphine, also called microinduction. Injectable naltrexone can of course be a good long-term treatment, but it does not treat symptoms of withdrawal.

CATR: And what about alcohol and sedative withdrawal?

Dr. Rastegar: Benzodiazepines are the treatment of choice for alcohol withdrawal. We use a symptom-triggered protocol with a scoring system that we developed as an alternative to the familiar Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar). If the patient's withdrawal goes above a certain threshold, we give a benzodiazepine, usually diazepam. Diazepam is certainly not the only medication you could use, but I prefer long-acting agents because you don't have to medicate patients as frequently. The exception is in patients with severe liver disease, specifically those with decompensated cirrhosis or evidence of synthetic dysfunction (elevated PT, INR, or total bilirubin). In those circumstances, the standard practice is to use lorazepam (*Editor's note: For more about management of alcohol withdrawal, see our interview with Dr. Brian Fuebrlein in* CATR *Jan/Feb/Mar 2023*).

CATR: You developed a different scoring system to assess alcohol withdrawal severity?

Dr. Rastegar: Yes, we found that the CIWA-Ar didn't work well for us. It has 10 items, so it's cumbersome, and it relies on subjective measures like anxiety and nausea. Most of the items are scored on a 0–7 scale and the definitions of each score are not really spelled out; what differentiates a 4 from a 5 from a 6, for example? So, we developed the Brief Alcohol Withdrawal Scale (BAWS), which has five items: 1) tremor, 2) diaphoresis, 3) agitation, 4) confusion/disorientation, and 5) hallucination (Rastegar D et al, *Subst Abus* 2017;38(4):394–400). Each item is scored 0–3, with a maximum of 15. Higher scores trigger higher medication doses and more frequent patient assessment *(Editor's note: See the table for more details)*. It's been easy to implement and works well for us. At this point, it is the standard tool across the Johns Hopkins medical system. Importantly for your readers in particular, the scale has been validated for use in psychiatric settings as well (Elefante RJ et al, *J Addict Med* 2020;14(6):e355–e358).

"Withdrawal symptoms are not all that specific. You can't always say, 'This symptom is due to withdrawal from alcohol and this other symptom is due to withdrawal from opioids' when the patient has been using both substances. Irritability is probably a universal symptom during withdrawal, regardless of substance."

Darius Rastegar, MD

Brief Alcohol Withdrawal Scale and Treatment Algorithm

Symptom	Scoring
Tremor	0: None 1: Mild 2: Moderate 3: Severe
Diaphoresis	0: None 1: Mild 2: Moderate 3: Severe
Agitation	0: None 1: Mild 2: Moderate 3: Severe
Confusion/disorientation	0: None 1: Mild 2: Moderate 3: Severe
Hallucination	0: None 1: Mild 2: Moderate 3: Severe

Interpreting Score

Total Score	Medication (Diazepam)	Assessment
0–2	0	
3–5	10 mg	Reassess in 4 hrs
6–8	20 mg	Reassess in 2 hrs
9+	20 mg	Contact doctor

CATR: And what about sedatives?

Dr. Rastegar: You can certainly utilize benzodiazepines for people who are withdrawing from sedatives. That's one way to go, but for patients taking high doses of non-prescribed benzodiazepines, we find that a phenobarbital taper works better. Those patients are hospitalized, and we give a fixed dose taper starting with 100 mg doses and tapering down to 60 mg doses; we hold doses for sedation. (Kawasaki SS et al, *J Subst Abuse Treat* 2012;43(3):331–334).

CATR: The medications we've discussed so far are all CNS depressants. Providers may be concerned about giving agents with potentially synergistic CNS-depressing effects.

Dr. Rastegar: This may be a concern in theory, but I can't say that we find it to be much of a problem in practice. We do a lot of comanagement of withdrawals, so we are often giving benzos and/or phenobarbital along with methadone or buprenorphine, and if the patients are being carefully monitored, it's rarely problematic. Remember, withdrawals occur because patients have built up tolerance, and most of our patients have very high levels of tolerance. If anything, I think we more often undermedicate our patients. Sometimes a patient becomes sedated. If that's the case, back off on the dosage or just wait for them to become more alert. We are typically using symptom-triggered protocols anyway, so if the patient is sedated, they aren't going to get additional medication. On the other hand, if the patient is agitated and/or confused despite high doses of sedatives, they should be referred for ICU care.

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CATR: We have been primarily discussing hospitalized patients. Which patients can be treated on an outpatient basis?
Dr. Rastegar: Deciding on the proper setting is the first decision to make. Outpatient can be appropriate for patients who aren't at risk for severe or complicated withdrawal and who have a fairly stable living situation, particularly if there is another person at home who can help monitor them.
CATR: And how does your clinical approach differ in the outpatient setting?
Dr. Rastegar: In terms of alcohol withdrawal, the main difference is that I use symptom-triggered protocols in the hospital, which we have already discussed, and a standing benzodiazepine taper for outpatients. I typically use chlordiazepoxide for outpatient alcohol withdrawal, starting with a dose of 50 mg for a day or two and then going down to 25 mg for two to three more days. If the patient does not have a history of severe or complicated withdrawals, gabapentin 300–400 mg three times a day is a reasonable option as well. For opioids, the goal is still to get patients onto MOUD, regardless of treatment setting. The difference here is that outpatient methadone must be started at an OTP, whereas buprenorphine can be started in the ambulatory setting. Outpatient buprenorphine induction can be very successful and achieved in several ways (*Editor's note: See interview with Dr. Capurso in* CATR *Nov/Dec 2021*). But returning to the topic of comorbid withdrawal, I think it is quite challenging to manage withdrawal from multiple substances on an outpatient basis. For these patients, I would recommend inpatient or residential treatment, at least until they are stabilized.
CATR: What are some other important considerations when treating these patients?
Dr. Rastegar: We've talked about alcohol, sedatives, and opioid withdrawals already, and those are certainly the ones that need active treatment. However, we often forget that patients withdraw from stimulants, nicotine, cannabis, and even caffeine.
CATR: What should we do about these? We don't think of them as requiring specific treatment.
Dr. Rastegar: It's true that they don't require specific medications beyond simple comfort measures, but comfort measures are important to remember. Withdrawing from these drugs, which many of us don't even think of as having withdrawal at all, can be incredibly uncomfortable. Provide NSAIDs and acetaminophen if the patient has pain or a headache, give nicotine replacement, and provide a sleep medication if the patient has trouble sleeping. Not only does paying attention to these needs help the patient feel heard and validated, it may also help us avoid a patient leaving prematurely against medical advice. The key here is to talk to your patient, find out what they need help with, and strive to be as responsive as you can.
CATR: Thank you for your time, Dr. Rastegar.

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severity using a validated scale. In the hospital, the most commonly used scale is the Clinical Opiate Withdrawal Scale (COWS; www.tinyurl.com/427amss2). Patients undergoing home induction can use the Subjective Opiate Withdrawal Scale (SOWS; www.tinyurl.com/3wrb8frt). The second step is to start medication once the severity reaches a certain threshold (COWS or SOWS >8–10). This threshold indicates that the amount of residual opioid in the patient's system is low enough that taking their first dose of buprenorphine won't trigger additional withdrawal symptoms.

An alternative method for starting buprenorphine, termed microinduction, involves the gradual introduction of buprenorphine in very small doses while the patient continues taking opioid agonists. Buprenorphine is titrated up to an effective dose, usually over the course of a week or two, and then the opioid agonist is stopped. The main advantage of microinduction is the very low risk of precipitated withdrawal. The downside is that the procedure is relatively slow, leaving the patient undertreated and at higher risk of overdose during the week or two that it takes to complete.

See *CATR* Apr/May/Jun 2024 for more on buprenorphine induction procedures.

If withdrawal occurs: Three options
Despite our best efforts, precipitated withdrawal will occur in a small subset of our patients. It is uncomfortable, sometimes intensely so, and can cause significant distress. While the research on how to treat precipitated withdrawal is sparse, there are three generally accepted approaches.

1) Symptomatic treatment
Opioid withdrawal symptoms include:

- Abdominal cramping
- Anxiety
- Diarrhea
- Insomnia
- Muscle aches
- Nausea
- Tachycardia
- Vomiting

Symptomatic treatment focuses on alleviating these symptoms through a combination of medications, each chosen to relieve a particular symptom. See "Symptomatic Treatment for Precipitated Opioid Withdrawal" table on page 5 for a rundown of medications that can be used to treat opioid withdrawal symptoms. The list may look familiar, as they are the same medications that are used to treat opioid withdrawal in patients who do not want medications for OUD (MOUD).

2) More buprenorphine
Giving the patient additional buprenorphine might initially appear counterintuitive, but it can ease withdrawal symptoms and make the patient feel somewhat better. The approach, akin to "ripping off the Band-Aid," floods opioid receptors with buprenorphine, and at a high enough dose it can provide adequate agonism to relieve at least some withdrawal symptoms. Evidence for this approach is restricted to

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a handful of case reports, but the studies indicate that an additional 8–16 mg of buprenorphine, given once precipitated withdrawal takes place, leads to symptom relief in one to two hours (Spadaro A et al, *Am J Emergency Med* 2022;58;22–26). This may seem like a high dose to give all at once, especially considering that guidelines typically recommend not to exceed 8 mg of buprenorphine in the first 24 hours (*Treatment Improvement Protocol 63*. SAMHSA; 2019). However, recent studies have shown that doses of buprenorphine as high as 32 mg are safe and well tolerated (Herring AA et al, *JAMA Netw Open* 2021;4(7):e2117128).

3) Switching to an opioid agonist

In cases where symptomatic treatment is insufficient or the patient is not amenable to taking additional buprenorphine doses, switching to opioid agonist treatment, namely methadone, can be effective. Studies have shown that buprenorphine and methadone both reduce morbidity and mortality associated with OUD (Santo T et al, *JAMA Psychiatry* 2021;78(9):979–993). Pivoting to methadone treatment may be a way of keeping your patient on MOUD after an unpleasant initial experience with buprenorphine.

If you decide to switch to methadone, it's important to consider the potential for QT prolongation. Whenever possible, obtain a baseline ECG, a set of blood chemistries, and replete potassium and magnesium in patients with potassium <4.0 or magnesium <2.0, which will lower the risk of a prolonged QT progressing to torsades de pointes. If these tests aren't immediately feasible, at the very least assess the patient's cardiac risk factors, monitor them as closely as you can, and obtain the labs and ECG as soon as possible.

To dose:

- A typical first dose is 20–30 mg
- 10 mg can be added if the patient is still in withdrawal (total of 40 mg in the first 24 hours after beginning treatment)

Remember that methadone must be prescribed by a federally regulated opioid treatment program (OTP) beyond the initial 72 hours. If you are going to start the patient on methadone, be sure that they will have access to an OTP going forward.

As-Needed Symptomatic Treatment for Precipitated Opioid Withdrawal

Symptom	Treatment
Abdominal cramps	Dicyclomine 10–20 mg Q6hrs
Anxiety	Hydroxyzine 25–50 mg Q6hrs *Lorazepam 1 mg Q4–6hrs; max 4 mg/day
Autonomic symptoms	Clonidine 0.1–0.2 mg Q1hr; max 0.8 mg/day
Diarrhea	Loperamide 4 mg, then 2 mg for each loose stool; max 16 mg/day
Insomnia	Trazodone 25–100 mg QHS Quetiapine 25–100 mg QHS
Muscle spasms	Methocarbamol 750–1500 mg Q8hrs Cyclobenzaprine 5–10 mg Q6hrs; max 30 mg/day
Nausea/vomiting	Ondansetron 4 mg Q6hrs; max 16 mg/day Prochlorperazine 5 mg QID
Pain/muscle aches	Acetaminophen 650–1000 mg Q8hrs Ibuprofen 400–600 mg Q6hrs

**Reserve for inpatient use*

Choosing between the three

Studies on treatments for buprenorphine-precipitated withdrawal are small, often lack control groups, and are frequently limited to case reports. No direct comparisons of different treatment strategies have been conducted. As a result, any of the three available options can be considered reasonable, each with its own pros and cons.

Symptomatic treatment focuses on alleviating discomfort but does not help the patient initiate MOUD. Adding more buprenorphine can relieve symptoms and expedite the induction process, but patients may be understandably hesitant to take additional doses. Switching to methadone effectively treats OUD but can complicate follow-up arrangements.

It's also important to note that symptomatic treatment can be combined with either of the other two options—patients can still receive medications for symptom relief even if they are given additional buprenorphine or switched to methadone.

Involve the patient in decision-making

Whenever possible, involve the patient in choosing a treatment path.

- Explain the risks and benefits of each approach
- Outline what each approach entails
- Ask which one they prefer

Because we have so few data, there really is no wrong choice.

Acknowledge patient experience

It is important to acknowledge the discomfort patients feel. Unfortunately, none of the strategies are likely to fully eliminate precipitated withdrawal symptoms once they start. But emphasize that the discomfort is temporary and that it should resolve in eight to 24 hours. After that time, patients will have started buprenorphine and can be titrated up to an effective dose with no fear of further precipitated withdrawal (Spadaro et al, 2022).

CARLAT VERDICT

Precipitated withdrawal can occur when buprenorphine is given while the patient still has an opioid agonist in their system. Various strategies can be used to minimize the risk of precipitated withdrawal, but it will inevitably happen from time to time. When it does, offer symptomatically targeted treatments, give additional buprenorphine up to 16 mg at a time, or switch to methadone. Reassure the patient that the discomfort is temporary, and don't discontinue MOUD.

Q&A With the Expert

Navigating Cannabis Withdrawal

Alan J. Budney, PhD

Professor of Psychiatry; Professor of Biomedical Data Science; Geisel School of Medicine at Dartmouth, Lebanon, NH.

Dr. Budney has served as a scientific advisor for Jazz Pharmaceuticals and Indivior Inc. Relevant financial relationships listed for the author have been mitigated.

CATR: Can you define cannabis withdrawal and tell us about its symptoms?
Dr. Budney: Cannabis withdrawal starts 24–48 hours after somebody stops cannabis. The symptoms can vary, but there is a "core" of common symptoms that are shared between withdrawal syndromes from other substances—irritability, sleep issues, mood issues, and appetite changes. Specific to cannabis withdrawal, people tend to lose their appetite. Some report strange dreams, though I think many of those cases are probably people starting to dream again. Cannabis tends to suppress dreaming. Physical symptoms include nausea, headaches, and hot flashes, which are usually fairly mild. On occasion, people will have more severe symptoms. When that happens, they usually involve nausea or stomach distress.
CATR: Is withdrawal severity dose-dependent?
Dr. Budney: We don't really know. Studies tend to have sample sizes of only a few dozen participants, so differentiating withdrawal severity between them is hard, especially because participants tend to be a uniform population of people who use fairly heavily. One would expect a dose-dependent effect physiologically, but it's not that clean-cut. In fact, it is not so clear with tobacco, opiates, or any other substance either. Anecdotally, we see huge individual differences that would be difficult to accurately predict. Plenty of people who use large amounts of cannabis have little or no withdrawal, while others who use a moderate amount may have fairly severe symptoms.
CATR: How long does cannabis withdrawal last?
Dr. Budney: At least in lab studies, most people start to feel better within a week, and symptoms are gone after two weeks. The symptom that lingers the longest is sleep issues. In our studies, we've followed people over a month and sleep never quite returned to baseline (Budney AJ et al, *J Abnorm Psychol* 2003;112:393–402).
CATR: THC is lipophilic, so it's stored in the body for a long time. Do you think THC's lipophilicity has anything to do with the time course of withdrawal?
Dr. Budney: I don't think it has great influence. THC may be detectable for a long time, but what matters are the physiological and behavioral effects of the drug—for THC, those last for a few hours. I referred to "core" withdrawal symptoms earlier, which are symptoms that occur in most, if not all, of the substance withdrawal syndromes. Even when drugs have very different mechanisms of action, these core withdrawal symptoms are shared. That's because withdrawal syndromes have as much to do with the brain's reward system as the effects of the drugs themselves. It's not about an opioid receptor versus a cannabinoid receptor—it's a withdrawal from reward. When you take a regularly recurring, potent reinforcer away, many patients experience irritability, depression, and disturbed sleep. There are a few drug-specific symptoms that have to do with how the drug functions in the body: pain and achiness in opioid withdrawal, seizures and tremor in alcohol withdrawal. But otherwise, most withdrawal symptoms are common across drugs.
CATR: Do these withdrawal symptoms interfere with someone's ability to cut back or stop using?
Dr. Budney: Most certainly. Think about it logically: If you're miserable and you know smoking a joint will take the misery away, that's going to make you more likely to smoke. And to my earlier point about core symptoms, patients report that withdrawal challenges their ability to stay sober from all substances, not just cannabis. We've done outpatient studies of cannabis withdrawal in which we keep in touch with the participant's significant other. Several times a participant's partner contacted us and pleaded, "Please let him go back to smoking. He's driving me crazy. He's so much more likable when he's smoking." Again, this doesn't happen to everybody, but the withdrawal is a big challenge for some.
CATR: How do you discuss withdrawal with patients? I imagine some haven't heard of it.
Dr. Budney: Most have experienced it themselves by the time they get to treatment. For those who are unfamiliar, we explain the symptoms, let them know what they may experience, and reassure them it's normal and will go away if they can abstain long enough. I've never had anyone who was shocked to learn about cannabis withdrawal. I think pretty much everyone is familiar with the fact that quitting tobacco smoking can be difficult, largely because of withdrawal symptoms. So I sometimes draw parallels there, pointing out the opposite appetite effects. In fact, we've compared cannabis and tobacco withdrawal in the laboratory and found that the discomfort and the irritability are about the same. About half of people have more withdrawal from tobacco and about half have more withdrawal from cannabis (Budney AJ et al, *Subst Abuse Treat* 2008;35:362–368).
CATR: Does the similar withdrawal severity from tobacco and cannabis translate into the two being equally difficult to quit?
Dr. Budney: For people in our study who used both, tobacco came out as a little harder to quit than cannabis. However, participants tended to have smoked tobacco for a longer duration and more frequently than cannabis. It's common to smoke one pack of cigarettes per day—that's 20 times per day. People rarely smoke cannabis 20 times a day.

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Expert Interview – Navigating Cannabis Withdrawal

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CATR: The development of easy-to-use and easy-to-conceal vaping devices must lead to higher THC consumption.

Dr. Budney: That's probably correct. It likely translates into worsening withdrawal syndromes overall, but there aren't many recent clinical trials being done with cannabis users looking to quit. However, we know that the amount of THC people are taking in is quite high. We are investigating how much THC people are consuming in the "real world" by recruiting participants via social media. These are mostly daily users, and they are taking in much more THC than we anticipated. Consequently, there appears to be a lot of tolerance because many seem to be functioning fairly well, at least by their self-reports.

CATR: How much THC are we talking about?

Dr. Budney: A conservative estimate of the mean amount of THC consumed daily by participants in our first study, which included over 3,200 daily cannabis users, was between 92 mg and 269 mg a day (Budney A et al, *Cannabis Cannabinoid Res* 2024;9(2):688–698). Another study we did found that 25% of participants reported 285 mg per day and 13% reported over 500 mg per day (Borodovsky JT et al, *Addiction* 2024; Epub ahead of print).

"Withdrawal should be a target along the path to change, but treating withdrawal has never been *the* answer for those seeking substantial change. We can get most people through withdrawal syndromes relatively easily; the key is what you do on the other side."

Alan J. Budney, PhD

CATR: Can you put these amounts into perspective?

Dr. Budney: Non-cannabis users will feel high from just 10 mg of THC, and most regular heavy users feel high at 20–30 mg. Most cannabis gummies are sold in 5 mg or 10 mg pieces. Smoking an entire 20% THC joint—the most common potency sold in dispensaries—delivers approximately 60 mg of THC. So, many people are taking in very large amounts of THC. This leads to the question of tolerance, something that has not been investigated thoroughly for cannabis. We have always known that tolerance develops, but now that people have easy access to high-potency cannabis products, it is becoming increasingly important to understand how much tolerance develops and how that affects behavior and cognition. We know that tolerance is a huge issue with opioids, of course, as it is for many substances. And returning to the topic of withdrawal, you would expect people who have developed substantial tolerance to be vulnerable to more severe withdrawal symptoms when stopping.

CATR: That's a big challenge in the cannabis literature: The cannabis being used in clinical trials is not the same as what people are using in the community.

Dr. Budney: That's true. In our studies that I referred to, we had many people reporting that they use 200–1000 mg of THC a day, but only a few cannabis self-administration studies have delivered over 120 mg (Schlienz NJ et al, *Drug Alcohol Depend* 2018;187:254–260). The cannabis provided to participants in research studies is generally much weaker than what is available at your local corner dispensary. I believe that the National Institute on Drug Abuse now can provide cannabis that is 9% THC, whereas the average potency of cannabis flower sold in shops is 20%, with concentrate products approaching 90% THC.

CATR: That must affect the generalizability of study results.

Dr. Budney: I'm sure it does to some extent. But even with research cannabis (6%–9% potency), participants report getting high. They report liking it. And until recently, in the alcohol literature, no one really studied blood alcohol levels (BAL) much over 0.100. We don't have studies with BAL over 0.20, which we commonly observe in practice.

CATR: You mentioned that withdrawal from cannabis can be variable. How common is it?

Dr. Budney: For daily cannabis users, I'd estimate 40%–70% will experience some degree of withdrawal, with lower estimates for those using less often (Bahji A et al, *JAMA Netw* Open 2020;3(4):e202370). And what about those consuming very high amounts of THC or using high-concentration THC products? We're not quite sure at this point how that translates into prevalence of withdrawal, but again, the assumption is that it likely increases the probability and severity of withdrawal experiences.

CATR: Is there a way to predict who is more likely to experience withdrawal?

Dr. Budney: It's similar to other substances. The more someone uses, the more likely they are to experience withdrawal. But there is going to be variability—you can predict risk to some degree, but accuracy is not going to be great. In my experience, the best way to predict is to ask the consumer. What happened the last time they stopped smoking? Did they have withdrawal symptoms? If they did, then they are likely to have them again.

CATR: What can we do for patients who experience cannabis withdrawal as a significant barrier to abstinence?

Dr. Budney: First, there is reassurance: Let them know withdrawal symptoms are expected, are normal, and don't last forever. Beyond that, general wellness advice can go a long way: Get exercise, drink plenty of water, and practice good sleep hygiene.

CATR: Are there specific treatments?

Dr. Budney: Most recently, researchers have been investigating novel agents specific to the cannabinoid signaling pathway, but there is nothing ready for clinical use (Haney M et al, *Nat Med* 2023;29(6):1487–1499). The most typical approaches are reassurance and basic behavioral strategies to treat symptoms. However, multiple medication approaches have been investigated with some promising results (Connor JP et al, *Addiction* 2022;117(7):2075–2095). Many consumers use cannabis as a sleep aid, so insomnia can be a real issue during withdrawal. These patients can benefit from a mild sleep medication to help get them over the hump. Irritability and anxiety might be treated with alpha-2 agonists like guanfacine. Depressed mood and anxiety can be treated with selective serotonin reuptake inhibitors. Turning to GI issues, some patients get so nauseous

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What to Expect When You're Expecting Withdrawal

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Mr. Hendrickson and Dr. Capurso have no financial relationships with companies related to this material.

Withdrawal syndromes differ in their time course and symptomatology depending on the type, amount, and duration of the substance used. These syndromes can range from mild discomfort to severe, life-threatening conditions requiring inpatient medical care. This article outlines the physiological mechanisms and expected time course of withdrawal syndromes for the most common substances, providing a clear picture of what clinicians can expect and how best to support patients through this process.

The physiology of withdrawal

Chronic substance use can lead to tolerance, a physiological state in which the body adapts to the constant presence of a drug, requiring progressively higher doses to elicit the same pharmacologic effect. This adaptation alters the body's equilibrium, leading it to depend on the drug's presence for normal functioning. When a patient abruptly discontinues the substance, this equilibrium is thrown off balance, leading to a withdrawal syndrome.

Withdrawal syndromes vary depending on the substance, as each drug exerts its own effects on the brain and body. The onset, duration, and severity of withdrawal are dictated by the drug's mechanism of action, such as whether it enhances or inhibits certain neurotransmitters, and its pharmacokinetics.

GABAergic agents: Alcohol and benzodiazepines

Alcohol and benzodiazepines work by enhancing the effects of GABA, an inhibitory neurotransmitter. Prolonged use results in the brain establishing a new equilibrium in the presence of chronic GABA inhibition, resulting in heightened excitability if the substance is abruptly removed.

Common symptoms of withdrawal

- **Mild to moderate symptoms:** Anxiety, insomnia, nausea/vomiting, sweating, tremors, headaches, and tachycardia.
- **Severe symptoms:** Hallucinations, seizures, delirium tremens (DTs; severe confusion, agitation, widely fluctuating vital signs).

Timeline of alcohol/benzodiazepine withdrawal

The following is a typical timeline for alcohol withdrawal. Benzodiazepine withdrawal follows a similar progression, but the time course varies depending on the half-life of the specific medication, stretching longer for agents like clonazepam and diazepam, and shorter for agents like alprazolam and oxazepam.

- **6–12 hours:** Early symptoms, including tremors, anxiety, nausea/vomiting, tachycardia, and hypertension.
- **12–24 hours:** Peak hallucinations risk. Early symptoms such as tremor and anxiety can escalate. Patients are usually fully oriented.
- **24–48 hours:** Peak seizure risk. Hallucinations may continue. Patients may start to become confused.
- **48–72+ hours:** Peak risk for DTs. Patients can become severely disoriented and have swings in vital signs. DTs require hospitalization and can be fatal if not properly treated.

Risk factors

Patients with prior history of severe withdrawal, long-term use (>10 years), heavy use (>20 drinks daily), or underlying health conditions are at higher risk for severe withdrawal symptoms. The Prediction of Alcohol Withdrawal Severity Scale can be a quick way of quantifying risk of complicated withdrawal (www.tinyurl.com/2xunucwa).

Management and treatment

Begin by assessing the patient's risk level.

- **Low-risk patients:** Can be managed with observation or standing nonbenzodiazepine anticonvulsants such as gabapentin.
- **High-risk patients:** Inpatient care is recommended. Symptom severity can be measured using the revised Clinical Institute Withdrawal Assessment of Alcohol scale (CIWA-Ar; www.tinyurl.com/2pxtud7m), and treatment involves tapering medium- or long-acting benzodiazepines. Benzodiazepine withdrawal is managed by prescribing a medium- or long-acting benzodiazepine and slowly tapering over a few weeks in the outpatient setting.

Remember, even low-risk patients need careful monitoring. Withdrawal symptoms can escalate if they are undertreated, turning them from low-risk to high-risk patients. If your patient develops severe symptoms, do not hesitate to escalate treatment and refer to emergency services or to inpatient admission. For more on alcohol withdrawal, see *CATR* Jan/Feb/Mar 2023; for more on benzodiazepine withdrawal, see *CATR* Oct/Nov/Dec 2023.

Opioids

Opioid withdrawal, while rarely life-threatening, can be incredibly uncomfortable. The sudden drop in central opioid agonism leads to anxiety and dysphoria, while the decrease in peripheral opioid signaling causes the prominent GI symptoms that characterize opioid withdrawal. The level of distress that people experience can lead them to return to use and act as a significant barrier to maintaining sobriety.

Common symptoms of opioid withdrawal

- **Mild to moderate symptoms:** Mild anxiety, irritability, mild GI distress, tearing, runny nose, yawning, achiness, gooseflesh, dilated pupils.
- **Severe symptoms:** Severe anxiety, agitation, severe abdominal cramping, vomiting, diarrhea, widespread muscle pain.

Timeline of opioid withdrawal

- **6–12 hours:** Early symptoms appear for short-acting opioids (eg, heroin, fentanyl).
- **30 hours:** Symptoms begin for long-acting opioids (eg, methadone).
- **72 hours:** Peak of withdrawal symptoms.
- **1 week:** Symptoms are mostly resolved for short-acting opioids, while long-acting opioid symptoms begin to diminish but may persist for longer.

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What to Expect When You're Expecting Withdrawal

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Risk factors

As with alcohol and benzodiazepines, longer duration of use and higher doses are predictive of more severe withdrawal syndromes. The presence of high-potency agents like fentanyl and fentanyl derivatives in drugs from the street can increase the risk of severe withdrawal.

Management and treatment

Quantify withdrawal severity with the Clinical Opiate Withdrawal Scale (www.tinyurl.com/427amss2). The preferred approach is to start methadone or buprenorphine to control withdrawal symptoms and continue as long-term treatment for opioid use disorder. In cases where this is not an option, symptomatic treatment, including clonidine, can be used along with supportive care.

See *CATR* Nov/Dec 2021 for more on how to start buprenorphine and *CATR* July/Aug/Sept 2023 for more on choosing between buprenorphine and methadone.

Stimulants

Stimulants primarily work by increasing levels of dopamine and norepinephrine. Drops in these neurotransmitters do not cause the same dramatic withdrawal symptoms that alcohol, benzodiazepines, and opioids do. Stimulant withdrawal is not directly life-threatening, and treatment is largely supportive. Nonetheless, the sudden loss of the rewarding properties of stimulants means that withdrawal can be associated with severe depression and put the patient at an increased risk of returning to use.

Common withdrawal symptoms

- **Physiologic symptoms:** Hypersomnia, fatigue, slowed movements, muscle pain, headaches.
- **Psychological symptoms:** Depression, irritability, increased appetite, vivid dreams, difficulty concentrating, powerful drug cravings.

Timeline of stimulant withdrawal

A classic "triphasic" model of stimulant withdrawal remains a useful framework to understand the stages of withdrawal (Gawin FH and Kleber HD, *Arch Gen Psych* 1986;43:107–113).

- **The "crash":** The patient initially experiences hypersomnolence, exhaustion, hyperphagia, and severe depression. This phase starts within hours of cessation for short-acting stimulants like cocaine and within a day or two for longer-acting agents like methamphetamine.
- **Subacute withdrawal:** After a brief period of normalized sleep and mood, depression, anxiety, and strong cravings resurface, which can last for several months. This is the period of highest risk of returning to use.
- **Extinction:** Mood and sleep gradually stabilize, and cravings become episodic. This phase can last indefinitely, with the risk of relapse gradually decreasing over time.

Management and treatment

Treatment is mostly supportive.

- Encourage proper sleep hygiene, hydration, nutrition, and physical exercise.
- The subacute withdrawal phase requires careful relapse prevention strategies to maintain sobriety.

For more on stimulant withdrawal management, see page 10 for our latest research update on a novel inpatient protocol for methamphetamine withdrawal (Wilens TE et al, *J Addict Med* 2024;18(2):180–184).

CARLAT VERDICT

Withdrawal syndromes are complex and vary significantly based on the substance used, duration, amount, and patient characteristics. By understanding the expected time course of withdrawal and recognizing key risk factors, clinicians can offer appropriate medical interventions, provide anticipatory guidance, and ultimately support their patients' recovery.

Expert Interview — Navigating Cannabis Withdrawal

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that they have trouble eating. For these patients, we've found prochlorperazine can be helpful. After all, if you can't eat, you're not going to tolerate withdrawal for very long.

CATR: What about just giving the patient THC?

Dr. Budney: These days, many people have access to cannabis from dispensaries, though I wouldn't recommend going that route if someone is highly motivated to abstain. Constructing a careful taper schedule out of dispensary products is going to be challenging. Pharmaceutical cannabis formulations are available—nabiximols (Sativex), a mouth spray that contains THC and CBD, and dronabinol (Marinol) are examples. There has been interest and some research on this approach (Allsop DJ et al, *Clin Pharmacol Ther* 2015;97(6):571–574).

CATR: Why hasn't this approach become standard?

Dr. Budney: It's probably used outside of standard treatment settings all the time. But we must ask: What are the therapeutic goals? The goal shouldn't be just to relieve withdrawal. Most consumers are aiming for abstinence or substantial reduction in use. Sure, giving someone THC will help relieve withdrawal symptoms temporarily, but there is no indication that this will help them one or two months down the line. I've wondered to myself why so many people struggle to quit cannabis, since in many ways, cannabis use disorder is relatively less severe than most other substance use disorders. I think the answer lies with the fact that, just like other drugs or cigarettes, cannabis becomes ingrained in a person's lifestyle. We sometimes focus on withdrawal as *the* target. Withdrawal should be a target along the path to change, but treating withdrawal has never been *the* answer for those seeking substantial change. We can get most people through withdrawal syndromes relatively easily; the key is what they do on the other side. It's an important first step, but that's just what it is—a first step. We need to make sure that our patients understand this from the outset.

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

Research Updates

WITHDRAWAL

Methamphetamine Withdrawal Treatment

Maryam Soltani, MD, PhD. Dr. Soltani has no financial relationships with companies related to this material.

REVIEW OF: Wilens TE et al, *J Addict Med* 2024;18(2):180–184

STUDY TYPE: Retrospective quality assurance examination

Methamphetamine use has surged dramatically, with a 460% increase in stimulant-related overdose deaths from 2016 to 2021. Unlike opioids or alcohol, methamphetamine withdrawal does not cause severe medical symptoms such as elevated blood pressure, seizures, or delirium, which has led to a lack of specific treatment protocols. Nevertheless, individuals withdrawing from methamphetamines often experience significant irritability, agitation, depression, and intense drug cravings, making it a challenging condition to manage.

In this study, the authors aimed to develop a standardized approach for treating psychiatrically hospitalized patients with methamphetamine withdrawal that minimized the need for constant physician intervention. The protocol, outlined in the table, starts with a full physical exam and a large dose of ascorbic acid, which might protect against methamphetamine neurotoxicity (Huang YN, *Toxicol Appl Pharmacol* 2012;265(2):241–252). The protocol then centers on behavioral interventions, with additional medications available as needed. Focus groups assessed the feasibility and staff perceptions of the approach.

Unit staff received training on the effects of methamphetamine, withdrawal symptoms, and protocol specifics. They enrolled 23 participants, all single men with recent methamphetamine use admitted to the inpatient unit. There was no control group, meaning all participants received the protocol. Most participants (87%) had comorbid opioid use disorder (OUD), and a majority (91%) were experiencing homelessness. Behavioral interventions alone sufficed for about half of them (48%), while the other half (52%) required medication, the most common of which was quetiapine. An impressive 83% of the patients completed the protocol, with a mean withdrawal symptom duration of 2.6 days. Staff feedback was positive regarding both the behavioral and pharmacologic components, and they found the pre-implementation educational material particularly beneficial.

The study's biggest limitations are its small size and lack of a control group. The adherence rate of 83% is notable and exceeds the 70% adherence rates reported in other studies (Lappan SN et al, *Addiction* 2020;115(2):201–217). However, it is unclear how much of this success is attributable to the protocol itself versus other factors. Another potential confounding variable is that most participants had comorbid OUD and all of them were started on medication for OUD (MOUD). While comorbid OUD is common among methamphetamine users, the impact of MOUD on the study's outcomes remains uncertain.

CARLAT TAKE

This small, non-controlled study introduces a novel clinical approach for managing methamphetamine withdrawal, an increasingly prevalent and challenging clinical scenario. Despite the study's significant limitations, its approach is valuable in light of the absence of widely accepted protocols for methamphetamine withdrawal treatment.

Methamphetamine Withdrawal Protocol

Admission Orders	
Comprehensive medical exam	Emphasis on vitals, heart and lungs, dental care, skin excoriations/infections
Ascorbic acid	1000 mg BID for 48 hours
Behavior-Based Orders	
Food and fluid intake	Encourage full meals and hydration; hold meal for later if patient misses meal
Sleep	Allow patient to sleep as they desire, even if it means missing unit activities
Exercise	Encourage physical activity
Medication Orders	
Insomnia	Mirtazapine 15–30 mg QHS
Panic or anxiety	Chlordiazepoxide 25 mg TID PRN; avoid standing benzo administration
Mild anxiety	Diphenhydramine 25 mg QID PRN; hold for disinhibition
Moderate and severe anxiety	Quetiapine 25–50 mg TID PRN
Worsening hallucinations or hallucinations with aggressive or self-harming content	Contact MD/NP

OPIOID USE DISORDER

Long-Term Patient Outcomes With Buprenorphine for Opioid Use Disorder

Peter Farago, MD. Dr. Farago has no financial relationships with companies related to this material.

REVIEW OF: Hasan MM et al, *Am J Drug Alcohol Abuse* 2022;48(4):481–491

STUDY TYPE: Retrospective analysis

Of the three FDA-approved medications for the treatment of opioid use disorder (OUD), buprenorphine holds particular promise given its efficacy, ease

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CE/CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com to take the post-test. You will be given two attempts to pass the test. You must answer 75% of the questions correctly to earn credit. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) *AMA PRA Category 1 Credits*™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

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 is a primary concern when treating patients for opioid withdrawal with buprenorphine and alcohol withdrawal with benzodiazepines simultaneously (LO #1)?
   [ ] a. Nausea and vomiting [ ] b. Delirium tremens [ ] c. Hypotension [ ] d. Respiratory depression
2. Which of the following is a common symptom of cannabis withdrawal (LO #2)?
   [ ] a. Irritability [ ] b. Increased appetite [ ] c. Hallucinations [ ] d. Euphoria
3. What is the expected progression of symptoms in alcohol withdrawal (LO #3)?
   [ ] a. All symptoms tend to occur at the same time
   [ ] b. Seizure → Delirium → Tremor
   [ ] c. Tremor → Delirium → Seizure
   [ ] d. Tremor → Seizure → Delirium
4. True or false: A new protocol for methamphetamine withdrawal treatment directs clinicians to include a large dose of vitamin E in admission orders (LO #4).
   [ ] a. True [ ] b. False
5. Which symptom is specific to opioid withdrawal and not commonly seen in alcohol withdrawal (LO #1)?
   [ ] a. Tremors [ ] b. Dilated pupils [ ] c. Diaphoresis [ ] d. Tachycardia
6. Which nonpharmacologic approach is recommended to manage mild cannabis withdrawal (LO #2)?
   [ ] a. Prolonged bed rest [ ] c. Increased THC intake
   [ ] b. Exercise and sleep hygiene [ ] d. Nicotine patches
7. How long after the last drink does delirium tremens typically occur (LO #3)?
   [ ] a. 6–12 hours [ ] b. 12–24 hours [ ] c. 24–48 hours [ ] d. 48–72 hours
8. According to a recent study, what was the association between length of treatment with buprenorphine and hospitalization frequency (LO #4)?
   [ ] a. There was no significant association between length of buprenorphine treatment and hospitalization frequency
   [ ] b. Longer treatment with buprenorphine was associated with lower frequency of hospitalization
   [ ] c. Longer treatment with buprenorphine was associated with higher frequency of hospitalization
   [ ] d. Longer treatment with buprenorphine was associated with higher frequency of hospitalization for men and lower frequency of hospitalization for women

Research Updates

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of use, and ability to be prescribed in nonspecialist office settings. While the host of positive outcomes associated with its use give us plenty of reasons to start buprenorphine, much less work has been done around when, and if, it is safe to stop. We all have been asked by patients starting buprenorphine, "Do I have to take this medication forever?" The work here gives us some more data to help answer that question.

Researchers at the CDC and the Massachusetts Department of Public Health conducted a retrospective, longitudinal study of 2,572 patients with OUD who were prescribed buprenorphine. They divided patients into four groups: poor adherence, good adherence for <6 months, good adherence for 6–12 months, and good adherence for >12 months. Because the researchers were particularly interested in how patients did over the long term, they chose to examine time points 12 months after treatment discontinuation and 36 months after treatment initiation. The primary outcomes were all-cause hospitalization and emergency department (ED) visits.

The results were clear: Longer buprenorphine treatment was associated with fewer ED visits and fewer

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ADDICTION TREATMENT
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hospitalizations. Relative to the patients with good adherence for >12 months, the odds of hospitalization at 36 months following treatment initiation were 1.42 (1.09–1.82, p<.01) among patients with good adherence for 6–12 months, 1.83 (1.49–2.24, p<.001) among patients with good adherence for <6 months, and 2.71 (2.10–3.51, p<.001) among patients with poor adherence. Similarly, relative to patients with good adherence for >12 months, the odds of needing an ED visit 36 months after starting treatment were 1.30 (1.01–1.71, p<.01) among patients with good adherence for 6–12 months, 1.51 (1.22–1.87, p<.001) among patients with good adherence for <6 months, and 2.71 (1.30–2.19, p<.001) among patients with poor adherence.

The trends were similar when authors examined patients 12 months after treatment discontinuation.

CARLAT TAKE

As far as we know, there is no safe time to stop buprenorphine, or any other MOUD for that matter. But this study suggests that, at least within the first year of treatment, longer treatment duration is associated with better outcomes. So encourage your patients to stay on buprenorphine once they've started it.

Write for us! www.thecarlatreport.com/join