THE CARLAT REPORT
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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. Discuss the pharmacology of various stimulant medications and nonprescription stimulant drugs.
2. Describe various treatment modalities for stimulant use disorder.
3. Understand the theoretical underpinning and logistical basics of contingency management.
4. Summarize some of the findings in the literature regarding addiction treatment.

Overview of Stimulants

Michael Weaver, MD, DFASAM. Professor and Medical Director, Center for Neurobehavioral Research on Addiction at the University of Texas Medical School, Houston, TX.

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Drs. Weaver and Capurso have no financial relationships with companies related to this material.

Stimulants are a large class of drugs characterized by their ability to increase alertness, arousal, and attention. Some are effective treatments for psychiatric and other medical conditions, while others are only used illicitly. As a class, stimulants share the potential for addiction and carry the risk of potentially serious side effects. This article provides an overview of stimulants, available agents, relevant pharmacology, and approaches to managing patients with stimulant use disorder (StimUD).

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Highlights From This Issue

Feature article
Stimulant medications are widely used without a prescription for cognitive enhancement, weight loss, and recreation, especially among young adults.

Feature Q&A
There has been a concerning increase in deaths due to stimulants, necessitating the implementation of harm reduction measures when treating patients with stimulant use disorder.

Q&A on page 6
Contingency management is an effective treatment for stimulant use disorder that takes advantage of principles from operant conditioning.

Article on page 8
Stimulants come in prescription medications and nonprescription drugs, all of which operate by modulating central catecholamine levels.

Q&A With the Expert

Update on Stimulant Use Disorder

Brian Hurley, MD, MBA, FAPA, DFASAM

Addiction physician; President of the American Society for Addiction Medicine; Medical Director of the Bureau of Substance Abuse Prevention and Control, Los Angeles County Department of Public Health, Los Angeles, CA.

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

CATR: Start by giving us an overview of psychostimulants.
Dr. Hurley: There are three major categories of stimulants that are misused: 1) prescription stimulants, 2) illicitly manufactured stimulants, and 3) cocaine. Prescription psychostimulants, which are approved for the treatment of ADHD and misused when taken without a prescription or outside the dosing guidelines provided by a prescription, include methylphenidate and medications based on amphetamines. Illicitly manufactured methamphetamine is a major driver of increasing overdose deaths in recent years. The prevalence, especially of methamphetamine and cocaine, varies greatly by geography, with methamphetamines being by far the most common agent in the Midwest and West Coast of the United States and cocaine being more prevalent in the Northeast.
CATR: What are some of the pharmacological differences between these agents?
Dr. Hurley: Stimulants all work by increasing dopamine

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neurotransmission in the brain. There are many amphetamine and amphetamine-derived medications used for ADHD treatment like lisdexamfetamine, dextroamphetamine, and amphetamine salts. These agents all work by increasing the release of dopamine and norepinephrine as well as blocking their reuptake, though time of onset and duration of action varies. Lisdexamfetamine is a prodrug that metabolizes to amphetamine, so it works slower while amphetamine salts are much faster. Extended-release formulations of course will have longer half-lives. Methamphetamine is lipophilic, which means it absorbs into the brain very quickly, so the time of onset is very short and its effects are much longer than prescription amphetamine medications. Methylphenidate has a similar mechanism of action to cocaine, which inhibits dopamine reuptake out of the synaptic cleft. However, cocaine has a stronger effect, where the magnitude of the perceived reward with cocaine is going to be greater. Also, cocaine is absorbed very quickly, much more so than methylphenidate.

CATR: Other than mechanism of action, how do cocaine and methamphetamine compare?

Dr. Hurley: The biggest difference is how long they last. Cocaine lasts around 20 or 30 minutes. There is some variation between people, and the effects of injection or smoking tend to be shorter-lived than insufflation. But cocaine effects are generally brief. When somebody uses cocaine, they typically use several times in succession, maybe over the course of an evening or a day. Methamphetamine, on the other hand, lasts 12–15 hours after use—much longer. And when people use multiple times, that can result in half a week or more of not sleeping, not eating. In an emergency setting, cocaine intoxication might resolve in an hour or two, which is not the case with methamphetamine.

CATR: Is the time of duration related to the prevalence or severity of adverse effects?

Dr. Hurley: I think so. The longer half-life is a big reason why we are seeing such high rates of hemorrhagic stroke and heart attacks with methamphetamines, as well as drug-induced psychiatric issues, particularly psychosis. Do people still have those consequences with cocaine? Sure. I'm not saying cocaine is safe, but longer-acting stimulants have greater adverse effects on someone's health and function.

CATR: You mentioned that methamphetamines are a major driver of increasing overdose deaths. Why is that?

Dr. Hurley: This is the fourth wave of the overdose epidemic. In the third wave, prior to 2019 or so, we were already seeing many overdose deaths from fentanyl. But now we're seeing deaths from sedatives and stimulants piled on top of this already high overdose rate. *(Editor's note: For more on the waves of the overdose epidemic, see our Q&A with Dr. Ciccarone in* CATR *Jul/Aug/Sep 2023.)* As I mentioned, stimulants can certainly cause death on their own, usually by causing a cardiovascular event, but a lot of stimulant-related mortality comes from inadvertent exposure to fentanyl. Fentanyl is now being found in illicit stimulants and sedatives, usually without the knowledge of whoever is buying the drug, and there is something about the combination of these drugs that is particularly risky and dangerous.

CATR: How common is it to find fentanyl in stimulants or other nonopioid drugs?

Dr. Hurley: The short answer is that we don't know. But to optimize safety, we operate with the assumption that all methamphetamine and cocaine has fentanyl in it. Of course, this isn't true, and paradoxically, if it were true, the situation would be safer—stimulant users would have opioid tolerance, and we could treat everyone as though they had an opioid use disorder (OUD). And we've got treatments for OUD! So, it's not just the presence of fentanyl that is the riskiest part of using illicit stimulants; it's the unreliability of whether a drug contains fentanyl. A recent article examining drug seizure data found that the prevalence of fentanyl in methamphetamine and powdered cocaine was 12%–15%. But there was incredible variability between geographies.

CATR: Can you outline the treatment options for stimulant use disorder (StimUD)?

Dr. Hurley: Treatments for StimUD can be thought of in terms of the traditional biopsychosocial model. We have medications, various manualized

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psychotherapies, and—specific to StimUD—we have contingency management, which produces the most robust response. *(Editor's note: For more on contingency management, see our interview with Dr. DePhilippis in this issue.)* And while we don't have any FDA-approved medications, there are some effective off-label agents. Topiramate, naltrexone, bupropion, and mirtazapine all have evidence behind them. The combination of injectable naltrexone and high-dose bupropion seems to be particularly promising for methamphetamines (Trivedi MH et al, *NEJM* 2021;384:140–153).

CATR: What about prescribing stimulant medications to treat patients using cocaine or methamphetamines?

Dr. Hurley: That can be a thorny issue. There is some evidence for this practice, specifically methylphenidate for cocaine use and mixed amphetamine salts for methamphetamine (www.asam.org/quality-care/clinical-guidelines). The pharmacologic rationale is pretty straightforward: We're replacing a dangerous unregulated drug with a safer prescription medication. So, you might ask, "If methadone works for OUD, shouldn't any psychostimulant work for StimUD?" And while it's the same underlying principle, it's not that simple in practice. First, prescription stimulants are not benign and can be addictive themselves. And while they can be helpful, they simply aren't as successful for treating StimUD as buprenorphine and methadone are for OUD. But they can be helpful when used for the right patient with careful monitoring. We recommend that patients start with nonstimulant medications. If those don't work, the stance of the American Society of Addiction Medicine (ASAM) and the American Academy of Addiction Psychiatry (AAAP) is that if a clinician is going to use a psychostimulant outside of its FDA-approved indication to treat StimUD, that clinician should be a board-certified addiction physician or in direct consultation with someone who is.

"With stimulant use disorder, consider the harm reduction maxim: 'Meet people where they're at.' Do they have proper medical care? If not, think about the medical consequences of chronic stimulant use, like modifiable cardiovascular risk factors."

Brian Hurley, MD, MBA, FAPA, DFASAM

CATR: It's unfortunate this approach doesn't work.

Dr. Hurley: Things would be easier if it did. It's clear that opioid agonists are the best treatment for OUD, but that doesn't translate so cleanly with other addictions. However, that invites us to think about the addiction more comprehensively. Medications can help, but really our task is to figure out how to support patients as they navigate their lives. That means collaborating with patients to explore issues at home—do they have a support network? Do they have a safe place to live? What about work? Can I connect them with supportive employment, vocational rehab, peer support groups? If they are committed to abstinence, how do we continue to support that goal? But even if they aren't committed to abstinence, we have tools to help these patients too. That is what the harm reduction movement is about.

CATR: How can we apply harm reduction principles to StimUD?

Dr. Hurley: Think about the classic harm reduction maxim: "Meet people where they're at." Do they have proper medical care? If not, think about the medical consequences of chronic stimulant use. Begin with modifiable cardiovascular risk factors like cholesterol and blood pressure. Don't shy away from monitoring your patient's cardiovascular risks through routine bloodwork and prescribing antihypertensives and statins. First-line treatment for these conditions is straightforward, and we can always consult with a primary care, cardiology, and/or medical toxicologist colleague when we have any questions about cardiovascular risk factor management. Dental issues related to dry mouth are also common with ongoing psychostimulant use. Ask your patients about their teeth, look into their mouth if they are reporting issues, and if at all possible, refer them to a dentist.

CATR: What are some other harm reduction tools that you would recommend?

Dr. Hurley: There is a lot of focus in the harm reduction community around route of administration. It is safer to smoke a drug versus inject a drug because it is easier to titrate drug use when smoking. Injection is also associated with infections that result in abscesses or other soft tissue infections, potentially advancing to sepsis. So, clinicians should encourage that switch. But even if somebody is injecting, connect them to syringe service programs so they have access to sterile injection equipment. We already discussed how fentanyl is now being found in illicitly sold cocaine, methamphetamines, stimulant pills, and sedative pills. People who purchase nonopioid drugs from the street are at particular risk if they get an accidental fentanyl exposure because they don't have opioid tolerance. Anyone using these drugs should be offered fentanyl testing supplies, and I would argue that anyone using any category of intoxicants should be offered naloxone. Overdose rates are so high and such a threat to public health that universal naloxone access is a crucial public health strategy. So, I'll prescribe naloxone for patients being seen for "only" cannabis or alcohol use.

CATR: How can patients get their hands on harm reduction supplies?

Dr. Hurley: Naloxone is now over the counter, or it can be prescribed. Depending on where you are practicing, you may have access to local or state resources that can get harm reduction supplies to patients. But even if those aren't available, there are places online where patients can go to get harm reduction materials.

CATR: What resources would you recommend for clinicians interested in learning more?

Dr. Hurley: The ASAM and the AAAP have come together to publish a clinical guidance document that describes what clinicians should know about treating StimUD (www.asam.org/quality-care/clinical-guidelines). It's fairly comprehensive, so that is usually where I refer people first. For those interested in psychotherapy, I recommend looking up *The Matrix*

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Manual, which is a free resource put out by the Substance Abuse and Mental Health Services Administration that outlines how to do cognitive behavioral therapy for StimUD (www.tinyurl.com/zb7fkfwj).

CATR: Any closing thoughts?

Dr. Hurley: I'll close with one final point. There was a huge cocaine epidemic in the 1980s—we saw huge rates of cocaine use in the United States—and then the rates went down. They didn't go down because everyone died; they went down because many people were able to stop using. We are seeing a reemergence of stimulant use, largely driven by methamphetamines. Rates are going up. We are in a scary situation. But we can't forget that people do recover. About 75% of people with SUD at some point in their lives are able to recover (Jones CM et al, *Drug Alcohol Depend* 2020;214:108169). We have tools to help with that recovery: contingency management, cognitive behavioral therapy, high-intensity outpatient treatment, residential treatment, off-label medications. Stimulant use is challenging and can be dangerous, but it is not untreatable. Recovery is possible, and we owe it to our patients to offer the most effective, evidence-based tools at our disposal.

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

Overview of Stimulants

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A brief history of stimulants

Stimulants have been used since prehistoric times (Hagen EH and Tushingham S. The Prehistory of Psychoactive Drug Use. In: Henley TB et al, eds. *Handbook of Cognitive Archaeology*. New York, NY: Routledge; 2019:471–498). In modern medicine, their use dates to the 19th century, when they were prescribed for indications as varied as anesthesia, weight loss, and asthma. Famously, cocaine was even included in the original Coca-Cola. However, by the 1950s, the risk of addiction and other adverse effects became evident, leading to increasingly restricted access and culminating with the passage of the Controlled Substances Act in 1970 (www.tinyurl.com/578am5xn).

Recently, stimulants have been implicated in a growing number of drug overdose deaths. Since 2019, overdose deaths involving stimulants have risen annually, now comprising a third of all overdose deaths in the US (O'Donnell J et al, *MMWR* 2020;69:1189–1197). This "fourth wave" of the drug overdose epidemic is driven by the contamination of stimulants with fentanyl and its derivatives, exposing people unexpectedly to opioids. One study found fentanyl in nearly 10% of illicit stimulants, particularly cocaine and methamphetamine (Wagner KD et al, *Drug Alcohol Depend* 2023;252:110985).

Pharmacology

Most stimulants, whether FDA approved or used recreationally, increase levels of the catecholamine neurotransmitters dopamine and norepinephrine. Some have additional mechanisms of action, like the serotonin agonism of MDMA, while others, such as caffeine and nicotine, work altogether differently. Pharmacologic properties that influence the addictive potential of stimulants include:

Potency

High-potency stimulants are more reinforcing. For example, methamphetamine produces much more powerful dopamine release than amphetamine, contributing to its greater addictive potential (Goodwin JS et al, *J Biol Chem* 2009;284(5):2978–2989).

Pharmacodynamics

Stimulants with rapid onset and short duration of action tend to be more reinforcing. Smoked crack cocaine, which reaches the brain in less than 10 seconds and peaks within minutes, is more addictive than intranasal cocaine, which takes longer to be absorbed and lasts up to 30 minutes (Bravo RR et al, *Toxins* 2022;14(4):278).

Prescription stimulants

Prescription stimulants, primarily FDA approved for the treatment of ADHD, are based either on methylphenidate or on amphetamine. Methylphenidate comes in:

- Immediate-release forms (Ritalin, Methylin, Focalin)
- Extended-release forms (Concerta, Relexxii)
- A transdermal patch (Daytrana)

Amphetamines come as:

- A racemic mixture of amphetamine salts (Adderall, Mydayis)
- A pure form of the D-isomer (Dexedrine, Zenzedi)
- Lisdexamfetamine (Vyvanse), a prodrug metabolized into dextroamphetamine by enzymes in red blood cells

See "FDA-Approved Stimulant Medications" table on page 5 for an overview of FDA-approved stimulants.

Despite their effectiveness, these drugs have the potential for addiction and serious side effects. Before starting a stimulant, establish a firm diagnosis and inform the patient of the risks. Stimulants are associated with modest increases in heart rate and blood pressure, so a careful cardiac history is warranted. Consult a cardiologist before starting a stimulant in patients with:

- History of syncope
- Chest pain
- Severe dyspnea on exercise
- First-degree relative who had sudden cardiac death
- Tachycardia or irregular heart rate on cardiac auscultation
- Clinical signs or diagnosis of Marfan's syndrome (taller than expected, long extremities, hyperextendable joints, pectus deformity)

Finally, monitor for misuse and check your state's prescription monitoring program to ensure patients aren't "doctor shopping."

Illicit stimulants

The most common illicit stimulants include:

- Cocaine—Used intranasally, smoked as "crack," or injected.
- Methamphetamine—Often sold as "crystal meth" due to its glass-like appearance; has a longer half-life

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Overview of Stimulants

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than cocaine and a greater propensity to cause psychosis. Most frequently smoked but can be snorted and injected.

- MDMA—An amphetamine derivative with empathogenic and psychedelic properties. Usually taken by mouth.
- Synthetic cathinones ("bath salts")—Highly potent and often containing a mixture of drugs, leading to aggression and psychosis during intoxication. Usually smoked or snorted; can be injected, swallowed, or used rectally.

Psychoactive and physical effects

These stimulants produce a rush of euphoria, energy, and enhanced concentration. Effects vary by half-life—methamphetamine has a half-life of four to eight hours resulting in effects that can last a day or more, compared to cocaine with a half-life of 15–30 minutes and effects lasting not much beyond an hour. See "Stimulant Drugs Not FDA Approved or Rarely Used Medically" table for an overview of these drugs.

Unlike alcohol or opioids, people generally use stimulants intensely for a short period, called a "run" or "spree." The period following the run, the "crash," is characterized by depression, anhedonia, low energy, and cravings to use again Moreover, research suggests this risk is dose dependent, with higher doses associated with higher risk of psychosis (Moran LV et al, *Am J Psychiatry* 2024;181(10):901–909).

High doses can cause manic and psychotic symptoms that typically subside with abstinence but can persist for months, especially with more frequent use. Stimulant use is associated with primary psychotic disorders (Toscano ER et al, *Schizophr Bull* 2023;49(5):1269–1280). Chronic use can lead to dopamine depletion, resulting in a Parkinson-like syndrome, severe dental issues ("meth mouth"), and loss of body weight, particularly muscle mass. Cardiovascular consequences include hypertension, cardiomyopathy, and heart failure, as well as increased risk of myocardial infarction and stroke (Curran L et al, *J Am Heart Assoc* 2022;11(16):e023663).

Treatment

No FDA-approved medications exist for StimUD, but some agents show promise, including bupropion with and without naltrexone, mirtazapine, and topiramate (see *CATR* May/June 2021 for a review of medications for StimUD). Psychotherapy can be effective, particularly modalities that incorporate a behavioral component such as cognitive behavioral therapy and contingency management (see our interview with Dr. DePhilippis in this issue for more). Trials examining whether prescription stimulants can be used to treat StimUD have been mixed, with some showing small benefits and others not (Tardelli VS et al, *Psychopharmacology* 2020;237(8):2233–2255). Currently, there is no high-quality evidence to recommend this as a general practice.

Harm reduction strategies

Harm reduction measures can decrease the morbidity and mortality associated with stimulant use, regardless of whether your patient is ready for abstinence. They include:

- Drug testing—Fentanyl test strips are a quick and inexpensive way to test for the presence of fentanyl. Learn about fentanyl testing in *CATR* July/Aug/Sept 2023.
- Naloxone distribution—Provide naloxone in case of unintended opioid exposure.
- Safer use supplies—Sterile needles and new smoking equipment reduce the risk of HIV, hepatitis C, soft tissue infections, and burns.
- Never Use Alone hotline—Patients can call this number (1-877-696-1996) to send emergency services if needed.

FDA-Approved Stimulant Medications

Generic Name	Indication	Brand Names	Slang Names
Amphetamine	ADHD, narcolepsy	Adderall, Benzedrine, Dexedrine, Evekeo, Zenzedi	Bennies, dexys, black beauties, white crosses
Amphetamine (extended release)	ADHD, narcolepsy	Adderall XR, Adzenys, Dyanavel, Mydayis	
Benzphetamine	Weight reduction	Didrex, Recede	
Lisdexamfetamine	ADHD	Vyvanse	Vicky, V-twin
Methylphenidate	ADHD, narcolepsy	Focalin, Methylin, Ritalin	Vitamin R, smart pills
Methylphenidate (extended release)	ADHD, narcolepsy	Concerta, Focalin XR, Relexxii	Pineapple, skippy
Modafinil	Excessive sedation due to narcolepsy, obstructive sleep apnea, shift work disorder	Provigil	
Armodafinil	Excessive sedation due to narcolepsy, obstructive sleep apnea, shift work disorder	Nuvigil	

Stimulant Drugs Not FDA Approved or Rarely Used Medically

Generic Name	Method of Use	Notes	Slang Names
Cocaine	Intranasal, smoked, intravenous	More common in Northeast US	Coke, crack, snow, blow
Methamphetamine	Intranasal, smoked, intravenous	Common in Midwest and Western US	Crank, crystal, ice, meth, speed, uppers
Methylenedioxymethamphetamine (MDMA)	Oral or snorted	Has psychedelic properties; being investigated as a psychotherapy aid	Ecstasy, X, Molly, Adam
Synthetic cathinones	Usually intranasal	Can cause high levels of dissociation and aggression	Bath salts, ivory wave, vanilla sky

CARLAT VERDICT

Stimulants represent a broad array of substances, ranging from FDA-approved medications to highly potent drugs that are exclusively used recreationally. An understanding of the pharmacology, risks, and treatment options for stimulants is important when managing patients with StimUD. Whenever possible, use evidence-based treatments for these patients combined with effective harm reduction measures.

Q&A With the Expert

Contingency Management for Stimulant Use Disorder

Dominick DePhilippis, PhD

Deputy National Mental Health Director, Substance Use Disorders, Office of Mental Health, Veterans Health Administration, Department of Veterans Affairs.

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

CATR: Define contingency management for us.

Dr. DePhilippis: Contingency management (CM) is an evidence-based treatment with particular effectiveness for stimulant use disorder (StimUD). I like to say that everything you need to know about CM you already learned in Psychology 101. It's based on fundamental learning principles described long ago by B.F. Skinner. At its core, CM is the therapeutic application of operant conditioning.

CATR: Remind us of the basics of operant conditioning and tell us how they apply to CM.

Dr. DePhilippis: In operant conditioning, behaviors are shaped by the application of reinforcements and punishment. In CM, we are taking advantage of four features of operant conditioning. First, we use *positive reinforcement*, meaning we provide a reward, or incentive, when a patient engages in a desired behavior. In our case, that behavior is abstaining from drug use. And the longer they abstain, the bigger the reward. Second, if they use drugs—that is, they don't engage in recovery behavior—they get no reward. That takes advantage of the second feature of operant conditioning: *extinction*. This term describes how behaviors tend to die out if they are not reinforced. Third, we have a *mild punishment* in place. If the patient uses drugs, not only do they receive no incentive that day, but they also have their incentive amount reset to the beginning. And fourth is *negative reinforcement*. Negative reinforcement is when behaviors are encouraged through the avoidance of an unpleasant consequence—in this case, the reset of the reward.

CATR: How do these programs work logistically?

Dr. DePhilippis: First, we must decide what behavior we want to reinforce. For our purposes, that behavior is abstinence. Next, we must be able to tell whether a patient has engaged in that behavior. Fortunately, urine drug screens (UDS) with immediately available results accomplish this easily *(Editor's note: For more on UDS, see* CATR *May/June 2022.)* As an aside, I can't overstate the importance of immediately available results; learning is best when consequences are immediate. That's why we utilize immunoassay-based drug testing that gives results right away. So, we have our behavior and we have our means of monitoring it; now we apply the operant conditioning principles. If the patient is abstinent, meaning they test negative for stimulants, they receive an incentive immediately.

CATR: What kind of incentives are used?

Dr. DePhilippis: There are various possibilities, but the incentive must compete with the reinforcement associated with substance use. And that can be a tough sell. Substance use says, "I can make you feel really good. There may be consequences down the road, but right now you're gonna feel good." Recovery has an inherent disadvantage. Not only can it be uncomfortable in the moment, but it can also give you a more lucid, clear-eyed view of the devastation in your life brought on by substance use. So, the incentive we provide must be immediately reinforcing. It also needs to be broadly appealing. In the network of Veterans Administration (VA) hospitals, we have access to coupons for the Veterans Canteen Service. These coupons are legal tender that can be used to purchase all sorts of merchandise available through VA outlets—anything from coffee or a candy bar to a laptop computer or flat-screen TV.

CATR: And what about providers who don't have access to these coupons?

Dr. DePhilippis: Some research protocols use cash as an incentive, and that certainly meets our criteria of being broadly appealing. The concern with cash payments, of course, is that cash can be used to buy drugs or other materials that may complicate recovery, like tobacco or alcohol products, or it can be used for gambling. And while that is a reasonable concern, evidence suggests that it happens less than you might think. In fact, cash and noncash reinforcement conditions show similar rates of stimulant use when compared head-to-head (Festinger DS et al, *J Subst Abuse Treat* 2014;47(2):168–174).

CATR: Most clinics don't have the resources to provide cash to patients, either.

Dr. DePhilippis: That's very true. Gift cards are the most common alternative to cash. But sourcing gift cards can be a challenge as well. Funding meaningful incentives remains one of the greatest challenges to implementing CM more broadly. But even so, I would encourage your readers to investigate local resources because there are state and county grants out there that fund CM programs. For example, California has a particularly robust CM system in place (www.tinyurl.com/n6sucka2).

CATR: Critics of CM might say, "Why should we pay someone not to use drugs? They should be doing that anyway." How do you respond to that?

Dr. DePhilippis: I don't think this is a proper application of the word "pay." When I pay someone, I am compensating them for a task or a good that serves my best interest. I pay a mechanic to fix my car; I pay the store for groceries. But in CM, we're providing reinforcement to strengthen a behavior that's in the patient's best interest, not our own. So, referring to it as payment is not an accurate description. Furthermore, we know that managed contingencies, positive and negative reinforcement, extinction, and punishment are how we learn. In fact, that's a large part of how substance use disorders develop in the first place. We are simply leveraging these same contingencies in the interest of treatment.

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Expert Interview – Contingency Management for Stimulant Use Disorder

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CATR: You mentioned that CM is particularly effective for StimUD. Can you walk us through that evidence?

Dr. DePhilippis: The strongest evidence supporting the application of CM comes from a series of meta-analyses (Bentzley BS et al, *JAMA Netw Open* 2021;4(5):e218049). These studies have very reliable and consistent findings that CM is the most effective treatment modality for StimUD. In fact, the evidence is so robust that the American Academy of Addiction Psychiatry (AAAP) and the American Society of Addiction Medicine (ASAM) jointly published a set of clinical practice guidelines for the treatment of StimUD in which they identify CM as the very best treatment (www.tinyurl.com/mr2rxuun). In addition, an expert panel from the VA and the Department of Defense developed treatment guidelines for substance use disorder (SUD) and named CM as the treatment of choice for StimUD (www.tinyurl.com/78nwyam6).

CATR: What is it about StimUD that makes it so conducive to CM?

Dr. DePhilippis: That's a good question. Because CM is based on operant conditioning, you might expect it to be effective across the board: for alcohol use disorder (AUD), opioid use disorder (OUD), and so forth. However, one challenge is in the mechanics—namely, the importance of immediate incentives and reliably detecting whether someone has used drugs. A UDS remains positive for roughly 24–72 hours after use of stimulants. That's a convenient length of time. We can test a patient twice a week, which is a typical schedule, and we're surveilling a full week's worth of behavior. In other words, if a patient tests negative, we can be fairly confident that the patient has abstained for the past week. But let's look at alcohol. A breathalyzer will only remain positive for six to 12 hours after the last drink. So, if we're truly going to surveil for alcohol abstinence, we'd have to test the patient twice a day, which is impractical. There is some work being done with the biomarker ethyl glucuronide, but we don't have a reliable immediate test for it (McDonell MG et al, *Am J Psychiatry* 2017;174(4):370–377). On the flip side, a UDS for cannabis can remain positive for a month or more, so in that case, we're unable to get results about recent behaviors.

"Substance use says, 'There may be consequences down the road, but right now you're gonna feel good.' Recovery has an inherent disadvantage. It can be uncomfortable in the moment, and can also give you a more lucid, clear-eyed view of the devastation in your life brought on by substance use. So, the incentive we provide must be immediately reinforcing and broadly appealing."

Dominick DePhilippis, PhD

CATR: What about opioids?

Dr. DePhilippis: Implementing CM with OUD is complicated for a few reasons. First, opioids bought and sold on the street are a highly heterogeneous group of drugs: prescription pills, heroin, fentanyl, and fentanyl derivatives, in addition to other compounds like xylazine, kratom, and tianeptine. An effective CM program would need to surveil this entire spectrum, which would be a huge challenge. Second, CM targets abstinence as its recovery behavior. If a patient abstains, their tolerance drops. We could end up inadvertently increasing the risk of fatal opioid exposure if the patient ever uses again, and addiction is a relapsing-remitting illness by its nature. Finally, the evidence is clear that the most effective, life-saving treatments for OUD are the three FDA-approved medications: methadone, buprenorphine, and extended-release naltrexone. Not only are those treatments effective, but they also offer a measure of safety because they protect against overdose. CM can't offer that.

CATR: And StimUD doesn't have the same medication options that OUD and AUD have.

Dr. DePhilippis: That's right. In fact, there are no FDA-approved medication options at all. There are some signals in the literature for pharmacotherapy, primarily for specific patient subgroups, but none of them are as effective as CM (Chan B et al, *Drug Alcohol Depend* 2020;216:108193).

CATR: What about false positive UDS results for stimulants?

Dr. DePhilippis: Yes, false results are challenges one must be prepared to address. With cocaine, false positives are rare, but with methamphetamine and amphetamine, the likelihood is greater. Trazodone and bupropion can cause false positives, and so can some patients' amphetamine medication for ADHD that is indistinguishable from other amphetamine use on the UDS. The consent process should make clear that self-report and clinician judgment don't have bearing on CM's reinforcement schedule; the UDS result is the sole determinant of reinforcement. Before starting, providers should review prescriptions and, if possible, make adjustments to minimize the risk of false results. If such changes are not possible or are unsuccessful, then the patient might not be a good candidate for CM. An alternative treatment, like cognitive behavioral therapy (CBT) for SUD, might be a better option.

CATR: What if you are working with a patient who isn't ready for abstinence? Is there still a place for CM in their treatment?

Dr. DePhilippis: What I'm hearing in that question is: "What about harm reduction? What about patients who don't embrace an abstinence model?" Well, the beauty of CM is that it does not compel a patient to embrace an abstinence goal. Instead, it suggests, "Dip your toe in the water; if you were to try abstinence for even a brief period of time, CM is there to provide reinforcement that could tip the motivational balance." The goal is for the patient to realize not only that they can do this, but that it's worth doing.

CATR: What are some remaining open questions in the field?

Dr. DePhilippis: One of the biggest challenges is knowing what level of incentive is necessary. I mentioned the state of California earlier. Well, California received a waiver to offer CM funded through Medicaid, and they

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Boost or Bust: Navigating the Risks of Prescription Stimulants

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Drs. Stiffler and Capurso have no financial relationships with companies related to this material.

Stimulants are first-line treatment for ADHD and generally considered safe and effective when properly prescribed. However, use of these medications without a prescription is widespread, particularly among college students and young professionals. In this article, we review the scope of nonprescribed stimulant use, discuss the potential dangers, and what to do if you run across it in your clinical practice.

How common is nonprescription use?

Age is the demographic factor most closely associated with nonprescription stimulant use. Such use is most common among young adults, particularly on college campuses, where half of students describe stimulants as "easy to get" (Weyandt L et al, *J Affect Disord* 2009:13(3):284–296).

We don't have high-quality data on how widespread the issue is across different settings, but the 2023 National Survey of Drug Use and Health found that 3.1% of adults age 18 to 25 and 1.2% of adults age 26 and older reported misusing stimulant medication (www.tinyurl.com/26pw5ah2).

Other factors associated with nonprescription stimulant use include:

- White ethnicity
- Male sex
- Membership in a fraternity or sorority
- Poor academic standing
- Poor executive or neuropsychological functioning
- Comorbid substance use disorder
- Poorly treated ADHD

(Source: Wilens T and Kaminski T, *Pediat Clin N* 2019;66(6):1109–1120)

What are stimulants used for?

Cognitive enhancement

The most common reason for nonprescription stimulant use is to enhance cognitive performance; users are seeking to improve focus, alertness, and productivity. The rationale is straightforward: Stimulants improve cognition in ADHD, so they must also help those without ADHD.

The research, however, doesn't quite bear this out. For example, a meta-analysis looking at stimulant effects in eight cognitive domains for participants without ADHD found that methylphenidate was associated with only slight improvement in three domains, modafinil had slight improvement in one domain, and amphetamines showed no improvements at all (Roberts CA et al, *Eur Neuropsychopharmacol* 2020;38:40–62). Another study in college students found that amphetamines produced only slight cognitive improvement in those without ADHD, but it had a large effect on subjective drug experience and positive states of activated emotion—in other words, students believed that the drug was much more effective than it was (Weyandt L et al, *Pharmacy* 2018;6(3):58).

Interestingly, there are suggestions that a person's belief about stimulants might provide more benefit than stimulants themselves. In one study, healthy college students engaged in cognitive testing after taking low-dose mixed amphetamine salts or placebo. Participants were unable to differentiate between the medication and placebo but performed better if they believed they were receiving active medication (Cropsey KL et al, *Drug Alcohol Depend* 2017;178:302–309).

Weight loss

Loss of appetite is a common side effect with these medications, so they are commonly taken without a prescription by those trying to lose weight. Studies show that people who use stimulants for weight loss are more likely to have other eating disorder symptomatology as well, such as use of laxatives, diet pills, or diuretics; purging; and higher-than-usual concerns about body image. One survey of 707 college students found that 4.4% of them reported using stimulants without a prescription to lose weight, with more than half of participants receiving the medication from a friend (Jeffers AJ and Benotsch EG, *Eat Behav* 2014;15(3):414–418).

Recreation

Stimulants are frequently taken without a prescription recreationally, usually in groups or at parties. Prescription stimulant users might enjoy a "high" with feelings of euphoria or increased energy. For those who drink alcohol, the energizing effects of stimulants may reduce subjective feelings of intoxication, allowing them to drink more or stay up later into the night (Egan KL et al, *Drug Alcohol Depend* 2013;131(1–2):71–77).

What are the risks?

Prescription stimulants are Schedule II drugs, defined as having "a high potential for abuse, with use potentially leading to severe psychological or physical dependence" (www.tinyurl.com/ydj7r3mz).

Stimulant use disorder

Nonprescription stimulant use can lead to the development of a stimulant use disorder (StimUD), although the prevalence of the disorder is unclear. Physiologic adverse effects range from mild—insomnia, irritability, tremors, and anorexia—to severe, including tachycardia, hypertension, and potentially fatal arrhythmias. Stimulants can cause psychiatric symptoms as well, particularly mania and psychosis (Moran LV et al, *Am J Psychiatry* 2024;181(10):901–909).

Seizures

Those using stimulants for weight loss can be particularly at risk of seizures, especially if they are engaging in other behaviors that could lead to electrolyte abnormalities with subsequent lowering of the seizure threshold, such as diet restriction, using laxatives, and purging.

Drug-drug interactions

People who use stimulants recreationally may be more prone to combine stimulants with other drugs, putting them at risk of synergistic adverse effects. For example, combining stimulants with alcohol can lead to increased levels of alcohol intake with less awareness of intoxication. Combinations with other

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illicit psychostimulants, such as cocaine and methamphetamine, could compound the risk of acute cardiovascular events (eg, cardiac ischemia, stroke).

What to do about nonprescription use?

Establish a diagnosis

Guidelines recommend that an ADHD diagnosis be established before a stimulant prescription is written (Faltinsen E et al, *BMJ Evid Based Med* 2019;24(3):99–102). As with any psychiatric disorder, diagnosis should be based on a detailed interview. For ADHD, gathering a developmental history that includes school performance is particularly important in establishing a firm diagnosis. If you are treating a child or adolescent, try to obtain collateral from caretakers and teachers.

Clinicians should not solely rely on manualized screening tools, though these can be useful to build up a fuller diagnostic picture.

Scales for young people include:

- Conners' Rating Scales (www.tinyurl.com/5d677buh)
- The Strengths and Difficulties Questionnaire (www.tinyurl.com/2m7ybwr3)

Scales for adults include:

- The Revised Adult ADHD Self Report Screening Scale (Ustun B et al, *JAMA Psychiatry* 2017;74(5):520–526)
- The Copeland Symptom List (www.tinyurl.com/yv46ardj)
- The Wender-Utah Rating Scale (www.tinyurl.com/wcpu4zx6)

For more on making an ADHD diagnosis, see our interview with Dr. Alyson Harrison in the January 2017 issue of *The Carlat Psychiatry Report*.

Look out for red flags

While you should exercise special care any time you are prescribing controlled substances, there are a few red flags that should make you particularly wary when it comes to stimulants:

- Patients requesting stimulants specifically, rather than ADHD symptom relief
- Patients unwilling to trial nonstimulant treatments
- Repeated requests for early refills
- Requests for ever-escalating doses
- Rapid weight loss
- Comorbid substance use disorders
- Unexpected negative urine drug screens

As always, check your state's prescription monitoring program to see if your patient is "doctor shopping."

Treat addiction

If you suspect stimulant misuse, ask your patient about it. Make sure they understand the risks and establish whether they meet criteria for StimUD. If they do, you should recommend that they receive proper StimUD treatment. There are no FDA-approved medications for this indication, though there are off-label options with evidence behind them, including topiramate, mirtazapine, bupropion, and the combination of bupropion and injectable naltrexone. Prescribing a stimulant medication as a treatment for StimUD is generally not recommended. Behavioral interventions and psychotherapy have the most evidence, including cognitive behavioral therapy and contingency management. For more on how to diagnose and treat StimUD, see *CATR* May/June 2021 and the accompanying articles in this issue.

CARLAT VERDICT

Stimulant medications are commonly taken without a prescription, especially among young people, for cognitive performance, weight loss, and recreation. Not only do stimulants have questionable benefits for those without a formal ADHD diagnosis, but they can have dangerous adverse effects. Restrict stimulant prescriptions to patients with an established ADHD diagnosis and provide addiction treatment for patients who meet criteria for StimUD.

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established their reinforcement level at $599 maximum per patient over the course of the study. This is because at $600 you trigger IRS reporting requirements, which obviously creates implementation challenges. But is $599 enough? We don't know. Some studies found that $500 is an amount that could effectively reinforce abstinence, but those studies are decades old (Petry NM. *Contingency Management for Substance Abuse Treatment: A Guide to Implementing This Evidence-Based Practice.* New York, NY: Routledge/Taylor & Francis Group; 2012:141). We likely need to increase the amount to accommodate for increases in cost of living, but we don't know how much is needed.

CATR: Over what time period is the money distributed?

Dr. DePhilippis: It varies. The $500 figure emerged from studies of 12 weeks in duration. The California program is $599 over 24 weeks. Veterans in our CM program typically earn $250–$300 over the course of a 12-week protocol.

CATR: These programs are all time limited. What happens afterward?

Dr. DePhilippis: Your question speaks to a common critique of CM: "Once you withdraw the reinforcement, you're going to have recurrence of symptoms." First, we don't level this criticism toward other chronic conditions. Imagine saying, "As soon you stop antihypertensive medication, blood pressure goes back up, so I guess antihypertensives aren't effective." No, that's not how it works. In fact, the recurrence of symptoms is evidence that the treatment did work. Am I suggesting that CM be unlimited? For some, maybe. What about for others? Surely the answer depends on the individual. Right now, we don't have the precision to identify who might benefit from what duration of treatment. But there is another concern here: Might we be decreasing our patients' own internal motivation toward abstinence? Well, I don't think so, and I'd argue that we are enhancing it. In fact, we have evidence that CM effects are durable beyond the protocol itself. Studies that follow patients after they have

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Research Updates

OPIOID USE DISORDER

Rapid Initiation of Extended-Release Buprenorphine

Aniruddha Deka, MD. Dr. Deka has no financial relationships with companies related to this material.

REVIEW OF: Hassman H et al, *Am J Drug Alcohol Abuse* 2023;49(1):43–52
STUDY TYPE: Open-label, prospective cohort study

The long-acting injectable form of buprenorphine, Sublocade (XR-BUP), is a promising alternative to sublingual formulations for the treatment of opioid use disorder (OUD), especially for patients who have challenges with adherence. However, the manufacturer recommends that patients be stabilized on a dose of sublingual buprenorphine for at least seven days before the first XR-BUP injection, a period that could lead to delays in treatment or dropping out of care. But is this waiting period necessary?

In this open-label study, researchers assessed the safety and tolerability of starting XR-BUP after a single 4 mg dose of sublingual buprenorphine. A total of 26 participants with moderate or severe OUD were recruited for the study. They stopped using opioids and were given a single 4 mg dose of sublingual buprenorphine once their COWS score was 8 or above. After one hour, as long as there was no precipitated withdrawal (defined as a ≥6-point increase in COWS score), researchers administered a 300 mg dose of XR-BUP. Participants were subsequently monitored as inpatients for 48 hours. Any residual withdrawal symptoms were treated with a small sublingual dose of buprenorphine or with symptom-specific medications (clonidine, ondansetron, NSAID, loperamide, etc).

Of the 26 participants who received the 4 mg sublingual dose, 24 received the XR-BUP injection. Overall, mean COWS score dropped from 14.6 ± 4.1 at the time of injection, to 6.9 ± 4.1 at six hours, to 4.2 ± 3.2 at 24 hours. Most participants (62.5%, n=15) experienced their most severe withdrawal symptoms prior to XR-BUP administration, though a minority (37.5%, n=9) did experience their most severe symptoms after getting XR-BUP. The patients whose symptoms were most severe after receiving XR-BUP experienced a slower overall reduction in COWS scores than those whose symptoms improved after receiving XR-BUP.

In total, 15 patients received sublingual buprenorphine or symptomatic treatment during the 48-hour observation period. Two patients met criteria for precipitated withdrawal after receiving XR-BUP; one had COWS scores increase from 15 to 22 over one hour and another had COWS scores increase from 3 to 11 over two hours. But even for these participants, COWS scores steadily declined over time. All participants had no active withdrawal or only mild symptoms by 12 hours after injection. There were no serious adverse events, and most tolerated the medication well. One month after the administration of the XR-BUP injection, 30% of the participants had opioid-negative urine samples.

CARLAT TAKE
This is a small open-label trial, so the results should be interpreted with a grain of salt, and the 48-hour inpatient observation period makes it impractical to duplicate this protocol in a clinical setting. However, the study does show that the full seven-day waiting period is probably unnecessary, affording providers more flexibility in formulating individualized treatment approaches.

SMOKING CESSATION

How Do We Help Depressed Smokers Quit?

Justin Morales, MD, and Deepti Anbarasan, MD. Drs. Morales and Anbarasan have no financial relationships with companies related to this material.

REVIEW OF: Cinciripini PM et al, *Depress Anxiety* 2022;39(5):429–440
STUDY TYPE: Randomized, double-blind, placebo-controlled trial

Like many addictive and psychiatric disorders, tobacco use disorder (TUD) and depression are comorbid. People with TUD and depression have worse health outcomes and have a tougher time quitting than their counterparts without depression. In addition, smoking itself is associated with more severe depressive symptoms. To better understand the safety and efficacy of medications for smoking cessation among depressed individuals, researchers reexamined a subset of data from the landmark Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial (Anthenelli RM et al, *Lancet* 2016;387:10037:2507–2520; see *CATR* November 2019 for more about the EAGLES trial).

This study included 2,635 participants with clinically stable major depressive disorder (MDD) and 4,028 participants without a psychiatric disorder, dubbed the nonpsychiatric cohort (NPC); all participants in both groups smoked 10+ cigarettes daily. Overall, there were slightly more females than males (56% vs 44%), and the average age was 47. As a group, the MDD cohort had smoked longer, had made more attempts to quit, and had more psychiatric comorbidities such as anxiety or history of suicidal ideation. Subjects were randomized to receive either varenicline, bupropion, nicotine replacement therapy (NRT), or placebo for 12 weeks, along with brief smoking cessation counseling. The primary safety outcome was occurrence of psychiatric symptoms such as mood, anxiety, or psychosis, termed neuropsychiatric adverse events (NAE). The primary efficacy outcome was smoking status during the final four weeks of treatment (weeks 9–12) and at six-month follow-up.

The safety analysis showed no difference between medications in rates of NAEs but did find that the MDD group had an overall higher rate than the NPC. Mild NAEs were common, with 41.1% of the MDD group and 29.5% of the NPC experiencing any NAEs. But they were generally tolerable, with only 1.8% of the MDD group and 0.7% of the NPC experiencing an event that was classified as serious or that led to medication discontinuation.

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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. What fraction of overdose deaths involve stimulants (LO #1)?
   [ ] a. One-fifth [ ] b. One-fourth [ ] c. One-third [ ] d. One-half

2. Which medication can be used to treat stimulant use disorder (StimUD) off-label (LO #2)?
   [ ] a. Citalopram [ ] b. Olanzapine [ ] c. Bupropion [ ] d. Buprenorphine

3. In contingency management (CM), what operant conditioning principle is applied when a patient does not receive a reward due to drug use (LO #3)?
   [ ] a. Positive reinforcement [ ] b. Extinction [ ] c. Mild punishment [ ] d. Negative reinforcement

4. True/false: Patients must be stabilized on a dose of sublingual buprenorphine for at least seven days before receiving their first extended-release buprenorphine injection (LO #4).
   [ ] a. True [ ] b. False

5. Stimulant use is associated with the development of which psychiatric disorder (LO #1)?
   [ ] a. Anxiety disorders
   [ ] b. Mood disorders
   [ ] c. Primary psychotic disorders
   [ ] d. Cognitive impairment

6. Which of the following is primarily responsible for the increase in stimulant-related overdose deaths (LO #2)?
   [ ] a. Polysubstance use
   [ ] b. Lack of FDA-approved medication
   [ ] c. Prescription stimulant misuse
   [ ] d. Fentanyl contamination of illicit stimulants

7. Which of the following is true about CM (LO #3)?
   [ ] a. CM is the best treatment for StimUD
   [ ] b. Evidence for the use of CM to treat StimUD is promising but in its early stages; off-label medications still have greater efficacy at this time
   [ ] c. CM is highly effective during treatment, but its benefits all but disappear a year after the incentives have been discontinued
   [ ] d. The drawback with CM is how costly it is to produce cash rewards for each patient

8. According to a recent study, what was the most effective method of smoking cessation in depressed patients (LO #4)?
   [ ] a. Smoking cessation counseling
   [ ] b. Bupropion
   [ ] c. Nicotine patch
   [ ] d. Varenicline

Research Updates

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You might expect that bupropion, being an antidepressant, would be most effective in the MDD group, but surprisingly, that is not what researchers found. In both cohorts, varenicline worked the best, bupropion and NRT were in the middle, and placebo was the least effective. Abstinence rates were slightly lower in the MDD group vs the NPC, but this difference did not meet statistical significance (p=0.101).

CARLAT TAKE

This study highlights that treatments for smoking cessation are safe and effective for patients with MDD, but the "two birds with one stone" approach of using bupropion for smoking cessation in your depressed patients is not the best way to achieve abstinence. Varenicline along with behavioral counseling is your best bet, with bupropion and NRT remaining viable second-line options.

Erratum: In our last issue, we reported on recent research examining the relationship between alcohol intake and all-cause mortality. We erroneously stated that underreporting alcohol consumption would underestimate mortality risk. Instead, we should have stated that underreporting alcohol consumption would overestimate mortality risk.

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completed CM have found enduring benefits for up to a year after incentives are discontinued (Ginley MK et al, *J Consult Clin Psychol* 2021;89(1):58–71). And when a course of CM is completed, the patient can receive other treatments like CBT.

CATR: What resources are available for those interested in learning more?

Dr. DePhilippis: I already mentioned the clinical practice guidelines put out by the VA and the Department of Defense, as well as the guidelines put out by the AAAP and the ASAM. Both are great resources and very comprehensive. I'd also point readers to educational materials put out by the Substance Abuse and Mental Health Services Administration through their Addiction Technology Transfer Center (www.tinyurl.com/6hd2vz89). Finally, the Northwest Addiction Technology Transfer Center has a set of asynchronous CM learning materials with modules designed for clinicians and program leaders (www.tinyurl.com/5a22yyva). These materials are not intended to be stand-alone training resources, but they can help a program do a deeper dive into what CM implementation entails.

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

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