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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Stimulant Use Disorder

Learning Objectives

After reading these articles, you should be able to:

1. Assess and treat patients with stimulant use disorders.
2. Identify potential misuse of loperamide, an over-the-counter antidiarrheal medication.
3. Summarize some of the findings in the literature regarding addiction treatment.

Pharmacotherapy for Stimulant Use Disorders

Rehan Aziz, MD. Associate Professor of Psychiatry and Neurology, Rutgers Robert Wood Johnson Medical School.

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

Stimulant use is surprisingly common. In 2017, 5.5 million people in the US took cocaine, and 757,000 of these people used crack. Another 5.1 million people misused prescription stimulants, representing nearly 2% of the total population (SAMHSA, 2019; www.samhsa.gov/data/). Many pharmacological trials for stimulant use disorder have been conducted, but they have yielded mixed results at best, and there are no FDA-approved agents for stimulant use disorder. However, some medications have shown promise, particularly in conjunction with psychosocial interventions, and we'll review them in this article.

Highlights From This Issue

We review the evidence in the confusing field of pharmacotherapy for stimulant use disorder.

Dr. Adriane dela Cruz walks us through best practice for working with patients with stimulant use disorders, from diagnosis through treatment planning.

Loperamide misuse?! Believe it or not, it's on the rise and can have dangerous consequences.

Medications

Antidepressants

Antidepressants are thought to work in stimulant use disorder by treating stimulant-induced depression and withdrawal dysphoria. A Cochrane systematic review looked at the evidence in cocaine use disorder (CUD) by appraising 37 randomized controlled trials with 3,551 total

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Q&A With the Expert

Diagnosing and Treating Stimulant Use Disorders

Adriane dela Cruz, MD, PhD

Assistant Professor of Psychiatry at UT Southwestern Medical Center, Dallas, TX.

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

CATR: Welcome, Dr. dela Cruz. Tell us what you do.

Dr. dela Cruz: I'm an assistant professor at UT Southwestern Medical School where I'm the adult psychiatry residency associate program director, and I teach medical students, residents, and fellows. Clinically, I'm an outpatient addiction psychiatrist where I treat a variety of patients with substance use disorders, many with medical comorbidities.

CATR: Could you take us through the treatment of a patient with a stimulant use disorder from the beginning?

Dr. dela Cruz: Obviously, the first step is diagnosis. It is important to ask about the different stimulants someone might be using such as methamphetamine, cocaine, or prescription stimulants. Ask about over-the-counter medicine like pseudoephedrine as well as bath salts and designer hallucinogens with stimulant properties. It can take a lot of questions to be certain what a patient is

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Mailing Information

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Pharmacotherapy for Stimulant Use Disorders

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participants. Studies included an array of antidepressants, most commonly bupropion, desipramine, and fluoxetine. Depression improved, but there was no reduction in cocaine use (Pani PP et al, *Cochrane Database Syst Rev* 2011(12):CD002950).

Although antidepressants are not particularly effective as a class in the management of stimulant use disorder, there is some evidence for mirtazapine in methamphetamine use disorder. Two placebo-controlled trials, both conducted in a population of men who have sex with men, demonstrated that 30 mg nightly dosing of mirtazapine modestly decreased methamphetamine use. The first study, which was relatively small at 56 participants, showed a decrease in methamphetamine-positive urine tox screens ($p = 0.04$) over 12 weeks when coupled with regular counseling (Colfax GN et al, *Arch Gen Psych* 2011;68(11):1168–1175). A larger, more recent study ($n = 120$) also showed a significant decrease in methamphetamine use that persisted out to 36 weeks ($p = 0.02$). Adherence in both studies was poor, however, and could present a challenge in the real world.

There might be new hope for bupropion in the treatment of methamphetamine use disorder as well. Recently, a large 12-week double-blind, placebo-controlled trial tested the combination of bupropion and naltrexone (Trivedi MH et al, *N Engl J Med* 2021;384(2):140–153). 628 adults received either extended-release injectable naltrexone (380 mg every 3 weeks) + oral extended-release bupropion (450 mg daily) or placebo. Patients who received the active drugs had fewer urine tox screens positive for methamphetamine than patients who received placebo, though the total number of negative tox screens was quite low in both groups (13.6% vs 2.5%). Mirtazapine and bupropion combined with naltrexone could be worth keeping in your back pocket. Give mirtazapine particular consideration if your patient struggles with insomnia or weight loss, which are both common in those who misuse stimulants.

Cocaine vaccine

Believe it or not, researchers have been developing a cocaine vaccine for years. The vaccine is supposed to work by producing cocaine-specific antibodies that block cocaine's passage into the brain, thereby preventing the reinforcing effects of drug use. Although an intriguing idea, results were largely negative in two large trials (Martell BA et al, *Arch Gen Psychiatry* 2009;66(10):1116–1123; Kosten TR et al, *Drug Alcohol Depend* 2014;140:42–47). Research continues, but as of now, the cocaine vaccine is not ready for clinical use.

Disulfiram

Disulfiram isn't just for alcohol use disorder (AUD) anymore—it holds promise for CUD, too. Recall that disulfiram causes an unpleasant reaction in patients who consume alcohol through its inhibition of acetaldehyde dehydrogenase. It also increases dopamine levels by blocking dopamine beta-hydroxylase. This could work to counter the dopamine depletion seen in chronic cocaine use and reduce cravings. Disulfiram also inhibits enzymes that metabolize cocaine. This leads to increased cocaine plasma levels, making cocaine use aversive.

Early studies with disulfiram were promising. However, it performed poorly in more recent studies, separating from

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Welcoming Our New Editor-in-Chief

We're pleased to introduce Noah Capurso, MD, MHS as the new editor-in-chief of *The Carlat Addiction Treatment Report*. Dr. Capurso is an assistant professor of psychiatry at the Yale University School of Medicine and practices clinically at the West Haven Veterans Administration Hospital. He attended medical school at Yale, where he received his MD, and where he conducted research in the Department of Biomedical Engineering. He stayed at Yale for residency and addiction psychiatry fellowship training. As an educator, Dr. Capurso teaches medical students about addiction treatment and develops the psychiatric curriculum for residents. As a clinician, Dr. Capurso is the medical director of the VA's Detoxification & Addiction Stabilization Service and the Psychosocial Residential Rehabilitation Program.

Expert Interview

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using, and I encourage providers to know local patterns of drug use. Urine drug screens are helpful for diagnosis and tracking treatment response. I don't use them for punishment, but as a way to determine if a treatment plan is working.

CATR: But urine drug screens don't detect all stimulants.

Dr. dela Cruz: That's right. Almost all include cocaine, which is detectable for 1–3 days and is straightforward because of its unique metabolic product benzoylecgonine, but other results require interpretation. Lots of medications like pseudoephedrine, phenylephrine, propranolol, and atenolol produce an amphetamine false positive. Even a confirmed positive amphetamine might mean prescribed amphetamine, lisdexamfetamine, or methamphetamine. Some, but not all, urine drug screens include a specific methamphetamine test. Methamphetamine is metabolized to amphetamine, so a patient who's using meth will be positive for both; it doesn't mean they are using multiple substances. Providers should get familiar with what their locally available screens test for.

CATR: What else should providers be paying attention to?

Dr. dela Cruz: A good skin exam is important, particularly for patients using intravenously. Subcutaneous injection and skin popping can lead to fat necrosis and cellulitis. There's a rare vasculitis associated with cocaine use, due to an adulterant called levamisole, that looks like a nonhealing open wound. I would recommend a dermatology consult if this vasculitis is suspected. And of course, people who use stimulants, and particularly those who smoke them, can have extremely poor dental hygiene from dry mouth and bruxism.

"There are no FDA-approved treatments at this point for patients with stimulant use disorders, but there is a lot of work being done in the field. Right now, my go-tos are mirtazapine or the combination of naltrexone and bupropion."

Adriane dela Cruz, MD, PhD

CATR: What are some of the demographic differences that you see across the stimulant use disorders?

Dr. dela Cruz: In terms of prescription stimulants, I see a lot of students, even early-career professionals. These people use them to stay awake, work, or party on the weekend. According to DSM criteria, tolerance and withdrawal do not apply to people taking stimulants as prescribed. Intranasal cocaine is seen among this group as well. Only about 15% of people who use cocaine or stimulants develop a use disorder, so there is a group who use cocaine casually without developing an addiction (Wagner FA and Anthony JC, *Neuropsychopharmacology* 2002;26(4):479–488). Crack use is seen more in an older urban population. Methamphetamine started as a rural drug but has become closely associated with sex work. In the population of men who have sex with men (MSM), there is a high prevalence of methamphetamine, ecstasy (also known as MDMA, 3,4-methylenedioxymethamphetamine), and GHB (gamma hydroxybutyrate).

CATR: Do you always test patients with stimulant use disorders for transmissible infections?

Dr. dela Cruz: Consider screening patients using a question like, "Have there been times in which you've had unprotected sex or sex with partners for whom you didn't know their STD status?" Intravenous drug use is also a risk factor, so ask about that. If there is concern, order a transmissible disease panel (HIV, hepatitis B and C, syphilis, gonorrhea, chlamydia) or consult the patient's primary care provider. This is also an opportunity to consider pre-exposure prophylaxis (PrEP) for high-risk patients *(Editor's note: For more on prophylaxis, see our Q&A with Sandra Springer, MD, in* CATR *Nov/Dec 2019).*

CATR: What are some practical differences to consider when treating patients with different stimulant use disorders: cocaine versus methamphetamine versus prescribed stimulants, for instance?

Dr. dela Cruz: The stimulants differ only slightly in their mechanisms, from a brain perspective. I wouldn't expect big differences in terms of response to medications.

CATR: And what are some of the medications that you've found to be most helpful for patients with stimulant use disorders?

Dr. dela Cruz: There are no FDA-approved treatments, but work is being done in the field. I was lucky to be part of the recent ADAPT-2 trial looking at the efficacy of the combination of 450 mg bupropion daily and 380 mg extended-release naltrexone every 3 weeks in patients with methamphetamine use disorder (Trivedi MH et al, *N Engl J Med* 2021;384(2):140–153). It's important to note that the naltrexone is given by deep intramuscular injection. The combination was more likely than placebo to decrease use and more likely to help patients achieve and maintain sobriety. Although the overall treatment response was relatively low (13.6% in the treatment group vs 2.5% in the placebo group), this trial is particularly clinically relevant because we evaluated the ability of the medications to help patients who are actively using decrease or stop, whereas many studies are relapse prevention trials. Mirtazapine is another good option. A recent trial by Phillip Coffin looked at mirtazapine in MSM (Coffin PO et al, *JAMA Psych* 2020;77(3):246–255) and found that mirtazapine 30 mg decreased methamphetamine use. So right now, my go-tos are mirtazapine or the combination of naltrexone and bupropion.

CATR: How would you evaluate the appropriateness of these medication options?

Dr. dela Cruz: Most psychiatrists are comfortable prescribing 30 mg of mirtazapine. Naltrexone and bupropion were well tolerated. You want to get a good seizure history before starting bupropion, especially since stimulants can predispose patients to seizures. Naltrexone can cause liver inflammation and should not be started in patients with transaminases more than 5 times the upper limit of normal or bilirubin elevation. Patients should have a platelet count 150 or higher because the medication is delivered by injection and there is concern that naltrexone could suppress platelets.

CATR: What about other medications like topiramate, n-acetylcysteine, disulfiram, or modafinil?

Dr. dela Cruz: There is lots of interest, but the data are mixed. There might be a role for lisdexamfetamine, which has been shown to decrease cocaine cravings (Mooney ME et al, *Drug Alcohol Depend* 2015;153:94–103). Other studies

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Expert Interview
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are ongoing, but doses are high in some of these protocols, up to 250 mg (Ezard N et al, *BMJ Open* 2018;8(7):e020723). Side effects included diarrhea, headaches, and anxiety. Modafinil has potential, but again, the data are mixed (Sangroula D et al, *Subst Use Misuse* 2017;52(10):1292–1306).

CATR: So it sounds like bupropion in combination with naltrexone, and mirtazapine are the top tier; perhaps modafinil and lisdexamfetamine are second line; and all the rest are third line.

Dr. dela Cruz: Yes. Keep in mind that the study investigated intramuscular naltrexone, so you have to have the capability to store and administer injections. For someone who's misusing prescription stimulants, I would favor lisdexamfetamine or modafinil as a way to stabilize them on a safe dose of prescribed medication, which they are taking anyway.

CATR: What about particular psychotherapeutic techniques?

Dr. dela Cruz: We need to acknowledge with our patients why it is that they use substances in the first place. I always ask, "What do you think the substance helps you with?" Surprisingly, many clinicians don't ask that. The answer to that simple question can be very revealing and help with treatment planning. For instance, you might discover symptoms that a patient is trying to treat, and a treatment plan will only succeed if these symptoms are addressed. A common answer is that stimulants help with social anxiety.

CATR: What's your response to that?

Dr. dela Cruz: I say, "Well, how are we going to create a treatment plan that lets you have social activities in a safe way and doesn't involve illicit drug use?" That can help set goals and allow for a therapeutic conversation, which should be balanced by motivational interviewing in which we examine the ways that drug use is harmful. If the patient does not reveal a particular motivation to change, I often ask, "What are your friends or family worried about?" and follow it up with, "Do you think those concerns have validity?" This can create that bit of cognitive dissonance we're looking for in motivational interviewing to help the patient acknowledge negative effects of substance use (*Editor's note: For more on motivational interviewing, see our Q&A with Carla Marienfeld, MD, in* CATR *March/April 2021).*

CATR: What other psychotherapeutic modalities have good evidence?

Dr. dela Cruz: There are a few big categories in addition to motivational interviewing. The first are 12-step programs/mutual help groups; Alcoholics Anonymous and Narcotics Anonymous are examples of these. Another is relapse prevention, which is derived from cognitive behavioral therapy (https://pubs.niaaa.nih.gov/publications/arh23-2/151-160.pdf). Making a thought record is core to relapse prevention. I'll begin with, "Tell me about the last time you used. What were the triggers?" Once we identify the events themselves, I ask, "What were you thinking? What were you feeling?" After identifying the factors leading to substance use, we brainstorm together about how to change the behaviors: "How can we approach that situation differently?" Finally, there is contingency management.

CATR: Contingency management has some of the best evidence.

Dr. dela Cruz: That's right. Contingency management is based on operant conditioning, the idea that reinforcers increase behavior. The targeted behavior here is sobriety. Some of the first studies in this area were conducted by Kathleen Brady (Killeen TK et al, *J Child Adolesc Psychiatr Nurs* 2012;25(1):33–41) in adolescents. Nancy Petry is a researcher in this area who has demonstrated contingency management efficacy in patients with stimulant use disorders (Petry NM et al, *Psychol Addict Behav* 2017;31(8):897–906). A typical model is a fishbowl full of raffle tickets in the clinic. Half the tickets say "good job," a third of the tickets award a small prize worth $1–5, a few are bigger prizes worth $20, and there is one ticket with a jumbo prize worth $100. Patients get to draw tickets if they have a negative urine drug screen. The first negative gets 1 draw, the next negative gets 3, and every subsequent negative test gets them escalating numbers of tickets up to a maximum point. But if they miss a visit or have a positive drug screen, it resets back to 1 draw. There are variations, but studies show that the prizes don't have to be especially valuable to support sobriety.

CATR: This can be difficult to establish in a typical clinical setting, though.

Dr. dela Cruz: True. It could be supported by a small grant since there is evidence that it works for relatively little money. I use an app called ReSET, which is an FDA-approved therapeutic. The patient needs a prescription in order to get access. Their website is www.resetforrecovery.com, where you get all the forms to prescribe the app. It includes therapy sessions, relapse prevention modules, and a built-in contingency management piece (*Editor's note: For more on ReSET and other apps as adjuncts for substance use treatment, see* CATR *Nov/Dec 2020).* The contingencies are small, but they can be quite powerful. It reminds me of similar contingencies in my own life. My fitness watch buzzes when I meet my step goal or calorie count for the day. It's important to get that pat on the back; it really does change behavior.

CATR: Recently we've seen a proliferation of easily obtainable designer drugs with stimulant-like properties, such as bath salts. Does the use of these substances manifest differently than the stimulants we've already discussed?

Dr. dela Cruz: There are no high-quality data, but it seems that bath salts are less common now than they were 5 or 10 years ago. Designer drugs and hallucinogens with stimulant properties are rising among young tech-savvy people who access the dark web.

CATR: How should providers approach patients who use bath salts or these designer stimulants/hallucinogens?

Dr. dela Cruz: Ultimately, these stimulants work similarly. We don't have evidence that these disorders should be treated differently from one another, at least pharmacologically. Behavioral interventions might differ depending on the drug, though. For example, an approach for a patient illegally purchasing methamphetamine might be to delete a drug dealer's contact information. Substances ordered off the dark web can be trickier—we can't tell patients not to go on the internet. But I do talk with patients about disabling portals they use to access the dark web. In addition, many of these drugs are bought using cryptocurrencies like Bitcoin, and I talk to patients about putting their Bitcoin into an electronic vault. You can get creative around placing roadblocks to drug access, even for drugs bought over the internet.

CATR: Thank you for your time, Dr. dela Cruz.

An Unexpected Opioid: Loperamide Misuse

Mara Storto, MD. Psychiatric Resident, Psychiatry Residency Training Program, New York University Langone Health, New York, NY. Deepti Anbarasan, MD. Clinical Assistant Professor of Psychiatry, New York University, New York, NY.

Dr. Storto and Dr. Anbarasan have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Loperamide, a common antidiarrheal available at pharmacies across the country, has unexpectedly become one of the latest in a growing trend of over-the-counter medications being repurposed for recreational use. Over the past 10 years, the broader public has discovered that supratherapeutic doses of loperamide can result in opioid-like euphoric effects. This information has been widely reported in internet forums that tout its use as a cheap "legal high." Unfortunately, in addition to euphoria, large doses of loperamide have been associated with cardiotoxicity, respiratory depression, and even death.

Indication and mechanism

Commonly known by the brand name Imodium, loperamide can easily be purchased without a prescription. We prescribe or recommend it for patients with ostomies, GI distress related to opioid withdrawal, some forms of chronic diarrhea, or run-of-the-mill occasional diarrhea. Many clinicians don't realize that loperamide is in fact a synthetic opioid. It slows down the gut by inhibiting intestinal peristalsis and allowing increased water absorption through its action as a mu-opioid receptor agonist in the intestinal tract, just like common opioids of abuse. Loperamide has historically been considered safe due to limited blood-brain permeability at its maximum recommended dose of 16 mg daily (Baker DE, *Rev Gastroenterol Disord* 2007;7:S11–S18). In other words, at therapeutic doses, loperamide does not act as an opioid agonist in the central nervous system, only in the gut, and therefore does not cause any of the analgesic or euphoric effects that we commonly associate with opioids.

Misuse

The significant GI distress that is experienced by patients in opioid withdrawal, characterized by diarrhea, nausea, and vomiting, can be treated appropriately with loperamide. Along with clonidine, ibuprofen, acetaminophen, and dicyclomine, loperamide is often a component of a symptom-based opioid detoxification protocol. In fact, it is thought that loperamide abuse first became widespread when patients taking it over the counter as a self-treatment for opioid withdrawal discovered that it could be taken regularly to keep withdrawal symptoms at bay. Given the inconvenience of daily methadone clinic visits, more and more posts on internet substance use message boards now recommend loperamide as a cheap and accessible alternative to methadone (Daniulaityte R et al, *Drug Alcohol Depend* 2013;130(1–3):241–244). Online users tout that supratherapeutic doses of loperamide (70–100 mg per day) result in central nervous system effects similar to methadone and can improve symptoms of opioid withdrawal. In fact, loperamide has recently come to be known as the "poor man's methadone."

Illicit drug websites discuss the use of "lope" at single doses of up to 400 mg to achieve an opioid high (the maximum recommended single dose is 4 mg). Once doses get above 25 times the recommended maximum daily dose, loperamide does cross the blood-brain barrier to achieve central nervous system effects, such as euphoria and analgesia. To further enhance these effects, users take loperamide in combination with P450 inhibitors that slow its metabolism and excretion, like quinine, quinidine, and cimetidine.

Studies looking at the number of calls to poison centers reporting loperamide overdoses, as well as analyses of Google search trends, have revealed the growing concern of loperamide's abuse potential (Borron SW et al, *J Emerg Med* 2017;53(1):73–84). From 2010 to 2015, there was a 91% increase in intentional loperamide exposures reported to the National Poison Data System—a worrying trend given the potentially lethal effects of loperamide taken at such high doses (Vakkalanka JP et al, *Ann Emerg Med* 2017;69(1):73–78). Loperamide manufacturers have gotten wary and capped the dose of a single pill at 2 mg. Packages typically contain loperamide exclusively in blister packs, and some pharmacies limit the number of packages that an individual can buy.

Side effects and toxicity

At recommended doses, the side effects of loperamide are mild and the medication is generally acknowledged to be safe. However, at the high supratherapeutic doses taken to achieve euphoria, frank opioid intoxication occurs with characteristic respiratory depression, pinpoint pupils, and sedation. Furthermore, like methadone, high-dose loperamide interferes with cardiac conduction and can cause dangerous arrhythmias. Many case studies have detailed QRS widening and QT prolongation, resulting in an increased risk of torsades de pointes (Marraffa JM et al, *Clin Toxicol (Phila)* 2014;52(9):952–957; Katz KD et al, *J Emerg Med* 2017;53(3):339–344).

Why is this important?

There is clear evidence of the rising popularity of loperamide abuse. As a result, in 2016 the FDA released a warning that high doses of loperamide can cause abnormal heart rhythms and serious cardiac events. Loperamide is not tested on the standard urine drug screen, so it is important for us to recognize and consider loperamide toxicity. In the case of acute toxicity, naloxone can be given for respiratory depression. Given the high risk of arrhythmias, these patients should be transferred to an inpatient unit with telemetry and receive a cardiology consultation (Eggleston W et al, *Clin Toxicol (Phila)* 2020;58(5):355–359). Unfortunately, we don't have any research about how best to treat patients with loperamide use disorder. It is unclear whether these patients require detoxification or whether buprenorphine, methadone, or naltrexone are helpful.

CATR VERDICT: Remain wary of loperamide abuse, particularly in patients with signs of opioid toxicity but a negative urine drug screen. Patients intoxicated on loperamide need inpatient admission and a cardiology consultation.

Pharmacotherapy for Stimulant Use Disorders

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placebo for length of cocaine abstinence and reduction in cocaine use in only one out of four trials. The studies, taken together, establish low-quality evidence to support the use of disulfiram (Ronsley C et al, *PLoS ONE* 2020;15(6):e0234809). You might keep it in mind, though, for patients who have failed other medications or for those with comorbid AUD.

GABAergic medications

GABA is the major inhibitory neurotransmitter of the CNS. By blocking activity of the dopamine reward system, GABAergic agents could prevent relapses by curbing stimulant-induced euphoria and reducing cravings. At least, that's the theory.

Topiramate is the best studied and has yielded mixed results; out of five studies; only two were positive. Those two found that at doses of 200 mg and 300 mg daily, topiramate promoted abstinence in cocaine, amphetamine, and methamphetamine use disorders (Ronsley et al, 2020). Like disulfiram, topiramate may be especially helpful in patients with comorbid AUD.

Modafinil

The theoretical underpinning of using modafinil for stimulant use disorder is appealing. As a mild stimulant, it increases dopamine, thus giving patients the boost of dopamine they are used to from stimulants.

However, in studies of CUD treatment, modafinil has had mixed results. A 2017 meta-analysis of 11 studies with 896 participants found that modafinil wasn't superior to placebo in improving treatment retention or achieving abstinence in CUD. However, a smaller subgroup analysis of six studies, conducted in the US, found that modafinil was superior to placebo in promoting cocaine abstinence ($p = 0.035$). The doses used in studies were well tolerated and varied between 200 mg daily and 400 mg daily, with most studies using 400 mg (Sangroula D et al, *Subst Use Misuse* 2017;52(10):1292–1306). High-dose modafinil is a reasonable option for stimulant use disorder, especially in patients with comorbid ADHD.

Stimulant substitution

Similar to methadone and buprenorphine for the treatment of opioid use disorder, and nicotine replacement for tobacco use, various psychostimulants have been tested as substitution therapy in patients with stimulant use disorder. These medications have similar mechanisms of action to the commonly misused stimulants but are safer and less habit-forming.

A 2016 Cochrane review examined psychostimulants and a few medications with stimulant-like effects in the context of CUD. It included 26 studies with 2,366 participants and assessed several medications: bupropion, dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil, methamphetamine, mixed amphetamine salts, and selegiline. Results indicated that, as a group, psychostimulants decreased relapse rates in participants already abstinent from cocaine ($p = 0.02$), though there were problems with the quality of the studies. Psychostimulants didn't reduce overall cocaine use or improve retention in treatment.

Looking at specific drugs, some stood out. Bupropion, dextroamphetamine, and mixed amphetamine salts were more efficacious than placebo in achieving sustained cocaine abstinence. Modafinil appeared to be more efficacious than placebo in reducing cocaine use. Lisdexamfetamine significantly decreased cocaine cravings compared to placebo.

However, since the number of studies investigating each drug was small, and treatment retention was a major issue, the overall quality of the results was compromised. While an intriguing option to keep an eye on, stimulant substitution isn't quite ready for prime time, at least not as a first-line treatment (Castells X et al, *Cochrane Database Sys Rev* 2016(9):CD007380).

Medications for Stimulant Use Disorders

Medication	Dosing	Special Considerations
Bupropion XL	450 mg PO qAM	• Good for comorbid ADHD, depression, nicotine use disorder • Risk of seizures • Risk of abuse • Combine with naltrexone (XR IM q3wks)
Disulfiram	250–500 mg PO daily	• Good for comorbid AUD • Risk of hepatotoxicity • Beware inadvertent reaction with alcohol, especially at high doses
Mirtazapine	30 mg PO daily	• Good for comorbid depression, insomnia, underweight
Modafinil	400 mg PO qAM	• Good for comorbid ADHD • Risk of abuse
Naltrexone	380 mg IM q3wks	• Good for comorbid AUD • Caution in patients with liver disease • Combine with bupropion
Topiramate	200–300 mg PO daily	• Good for comorbid AUD and weight loss • Cognitive clouding side effect • Risk of kidney stones, metabolic derangements

Approach

There are no clear-cut winners here, but based on the limited data we have and the safety profiles of the medications, the following could be considered for the treatment of stimulant use disorders:

- Modafinil
- Bupropion/naltrexone
- Mirtazapine
- Topiramate
- Disulfiram

Lisdexamfetamine is also an intriguing choice, though trials have used very high doses that, at this point, cannot be recommended for routine use.

CATR VERDICT: The evidence base for the pharmacologic treatment of stimulant use disorders is mixed, with only a few positive trials for a variety of stimulants. Though there are a few promising contenders, medications still serve primarily in a backup role. Consider comorbidities before prescribing.

CE/CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password and take the post-test. You will be given 2 attempts to pass the test. You must answer at least 75% correct to pass. 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. The Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. The Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credits*™ or 1 CE for psychologists. 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. In the ADAPT-2 trial, what did researchers conclude about the efficacy of the combination of buprenorphine and naltrexone for patients actively using methamphetamine, compared to placebo (LO #1)?
   [ ] a. The combination was more likely to decrease use and help patients achieve and maintain sobriety
   [ ] b. The treatment arm had an extremely high response rate
   [ ] c. There was no significant difference between the treatment arm and placebo on any outcome
   [ ] d. The combination had no effect on use frequency, but it did help patients achieve and maintain sobriety
2. For acute loperamide toxicity, naloxone can be given for respiratory depression (LO #2).
   [ ] a. True [ ] b. False
3. According to a 2020 study, what was the effect size of Improving Pain During Addiction Treatment (ImPAT) for pain tolerance in men at 3 months (LO #3)?
   [ ] a. 0.6 [ ] b. 0.18 [ ] c. 0.4 [ ] d. 0.81
4. Which of the following medications has the most evidence for promoting cocaine abstinence in patients with cocaine use disorder and comorbid ADHD (LO #1)?
   [ ] a. Topiramate [ ] b. Dextroamphetamine [ ] c. Modafinil [ ] d. Lisdexamfetamine
5. At supratherapeutic doses, what side effects does loperamide cause (LO #2)?
   [ ] a. Dangerous arrhythmias and seizures
   [ ] b. Hyperarousal and respiratory depression
   [ ] c. Respiratory depression and headache
   [ ] d. Dangerous arrhythmias and respiratory depression

Research Update

PAIN

A Psychosocial Intervention for Chronic Pain and SUD

REVIEW OF: Ilgen MA et al, *JAMA Psychiatry* 2020; published online July 29, 2020

Co-occurring substance use disorders (SUD) and chronic pain can be tough to treat. Little research has focused directly on this phenomenon, since most studies of pain exclude individuals with SUD. However, a few small, open studies of psychotherapeutic pain management in the presence of SUD have been promising.

In the current (2020) study, researchers tested a new psychosocial technique designed specifically for patients with co-occurring SUD and chronic pain. Improving Pain During Addiction Treatment (ImPAT) is a behavioral intervention that combines two techniques: cognitive behavioral therapy (CBT) and acceptance-based therapy. A pilot study in 2019 showed promise in using this technique for treating pain with opioid use disorder, and a large, randomized study of veterans with pain and SUD (Ilgen MA et al, *Addiction* 2016;111(8):1385–1393) found the intervention to be associated with decreased pain, increased functioning, and decreased alcohol use. However, the 2016 study's generalizability was limited in that it only included veterans and predominantly men. The current study was an attempt to extend those findings to the larger community, analyzed separately for men and women.

Patients were recruited from an abstinence-based, 60-day residential treatment program: Community Programs, Inc. in Waterford, Michigan. Medications for addiction treatment (MAT) were not offered in the program and were not included in the study design. Participants had severe SUD, involving primarily cannabis, opioids and alcohol for men, and opioids and cocaine for women, and all participants reported moderate to severe pain in the 3 months prior to the study. 510 individuals (48% women) were randomized to ImPAT or to a supportive psychoeducational control (SPC). Both interventions were manualized, and were provided by trained masters-level therapists, in 8 one-hour group sessions over 4 weeks. ImPAT highlighted the link between pain, functioning, and substance use and worked to explore new ways of conceptualizing and responding to pain while preventing return to substance use. SPC focused on topics like nutrition and the course of addiction, which were relevant to the patients but distinct from ImPAT. Follow-up assessments were done

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at 3, 6, and 12 months. Primary outcomes were pain intensity, pain-related functioning, and pain tolerance. Secondary outcome was frequency of alcohol and drug use. The study was funded by grants from NIDA and NIAAA.

The group sessions had good attendance, with 91.7% of participants completing the 12-month programs. Of the six outcome measures (three each for men and women), only two favored the efficacy of the intervention. Men showed increased pain tolerance throughout the follow-up period, and women showed decreased pain intensity at 12 months. However, there was no decrease in alcohol and drug use compared to the control group. The effect sizes for all outcomes were small: 0.4 for pain tolerance in men at 3 months, but otherwise not over 0.23 for any outcome.

A strength of the study was its control group, which was equivalent to the active treatment in format, intensity, and duration. A major limitation was the lack of MAT in either arm, which is a cornerstone of addiction treatment.

CATR'S TAKE

CBT and acceptance-based therapy alone, without medications, may not be effective for managing chronic pain and addiction together. It may be more effective if used in conjunction with MAT—future studies ought to address this.

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