THE CARLAT REPORT ADDICTION TREATMENT

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Noah Capurso, MD, MHS
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Cannabis

Learning Objectives

After reading these articles, you should be able to:

1. Differentiate between commercially available cannabis products.
2. Describe symptoms and treatment of cannabis withdrawal.
3. Utilize strategies for discussing medicinal cannabis use with patients.
4. Summarize some of the findings in the literature regarding addiction treatment.

Currently Available Cannabis Products

Special Double Issue! Worth 2 CME credits!

Alex K. Rahimi, MD. Addiction Psychiatrist, Fort Belvoir Community Hospital, VA. Assistant Professor of Psychiatry, Uniformed Services University, Bethesda, MD.

Dr. Rahimi, author for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

Cannabis use in the US is at an all-time high, serviced by a booming retail industry and supported by evolving state legalization. As society's stance on cannabis develops, so too have the forms and modes of cannabis consumption. Today, people walking into a cannabis dispensary have an enormous array of products to choose from. As providers, it's important to understand what is out there so we can have informed conversations with our patients. In this article, we'll begin with some cannabis basics and then take a look at what's on the market right now.

Highlights From This Issue

Feature article
Cannabis is commercially available in a wide variety of formulations, each of which has unique pharmacologic properties.

Feature Q&A
Cannabis withdrawal is common in patients with cannabis use disorder and can be an obstacle to recovery.

Q&A on page 6
There is no evidence supporting cannabis as an effective treatment for psychiatric disorders, despite numerous state approvals for medical use.

Cannabis basics

The cannabis plant contains more than 500 chemicals, about 100 cannabinoids and 400 non-cannabinoids (Rock

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Q&A With the Expert

Cannabis Use Disorder and Withdrawal

Denise Walker, PhD

Research Professor and Director of the Innovative Programs Research Group, School of Social Work, University of Washington, Seattle, WA. Co-developer of The Change Companies' What About Marijuana? *journal.*

Dr. Walker, expert for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

CATR: Please tell us about your work.
Dr. Walker: I'm a research professor at the University of Washington in the School of Social Work. I'm a clinical psychologist by training, and a large portion of my research focuses on cannabis use disorder (CUD) treatment.
CATR: Let's start by clarifying the term "cannabis."
Dr. Walker: The term cannabis can apply to any product that contains cannabinoids. But when we talk about cannabis here, we are referring to any cannabis plant material, or extract of that material, that contains THC, which is the psychoactive component in cannabis that produces a high. Another compound in cannabis that has garnered a lot of attention, cannabidiol (CBD), does not produce a high and, as far as we know, does not cause addiction or withdrawal. With over 100 cannabinoids present in the

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Mailing Information

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cannabis plant, there is still a lot to learn, but as far as we know, THC is the culprit responsible for CUD and withdrawal.

CATR: Can you define CUD? How does it compare with addiction to other substances?

Dr. Walker: CUD is problematic cannabis use that is persistent in the face of negative consequences. Those can be social consequences or negative impacts on physical or mental health. The criteria are really no different than for other substance use disorders (SUDs) such as alcohol, nicotine, cocaine, or opioid use.

CATR: My impression is that because CUD is associated with lower morbidity and mortality than, say, opioid use disorder, many people view cannabis as something not to be taken seriously.

Dr. Walker: Unfortunately, you're right. A common perception of cannabis is that you can't actually become addicted to it. We hear that all the time, even sometimes from medical professionals. But cannabis certainly can be addictive, and the research bears that out. It's important to check our social perceptions because it's easy to be sucked into whatever opinions are currently popular or reported in the media; those opinions might be widely held, but they are not necessarily scientifically informed. But just like other drugs, people can use cannabis occasionally without significant consequences and without developing an SUD. Figures vary, but as many as 30% of people who use cannabis develop CUD (Hasin DS et al, *JAMA Psychiatry* 2015;72(12):1235–1242). Of course, prevalence goes up for folks who use larger amounts, use more frequently, and have a younger age of first use (Millar SR et al, *BMC Public Health* 2021;21(1):997).

CATR: What risk factors put someone at risk of developing CUD?

Dr. Walker: Risk factors for CUD are similar to other addictive substances and include social, psychological, and biological factors. Level of THC exposure is a significant factor; greater frequency of use and higher THC concentration are both associated with the development of CUD. It's the same as with any other drug—the more your brain is exposed, the more opportunities there are to experience rewarding effects over time, potentially leading to addiction. Another risk factor is comorbid psychiatric illness. That includes other SUDs, psychosis, mood disorders, anxiety, and PTSD. Folks with these diagnoses all have higher rates of CUD than the general population (Borodovsky JT and Budney AJ, *Int Rev Psychiatry* 2018;30(3):183–202). Finally, people who primarily use cannabis to cope with painful or unpleasant emotions seem to be at greater risk for developing CUD. This pattern of use also tends to be particularly challenging to treat.

CATR: And yet, cannabis is approved for the treatment of many of the conditions you just named, at least in some states.

Dr. Walker: You're right. It's important to understand that authorization for medicinal cannabis comes from state legislators, not medical experts. Lawmakers typically get input from researchers, clinicians, and their constituents, but what they do with that information is up to them. So the presence of cannabis on a list of approved "treatments" does not mean that there is an evidence base to suggest that it is actually helpful. In the case of psychiatric illness, regardless of whether the CUD starts before the mental health disorder or vice versa, the two together lead to worse outcomes for the mental health disorder and the CUD. And controlled clinical studies have not found cannabis to be an effective treatment for any psychiatric disorder.

CATR: This situation really leads us to question the term "medical" cannabis, which is used all the time.

Dr. Walker: That's true; "medical" cannabis is a misnomer. And beyond that, the more you study cannabis, the more you realize how much blurriness there is between "medical" versus "recreational" use. In reality, people don't separate into tidy categories of using cannabis completely for the treatment of some condition or completely recreationally. We notice that most of the people who use cannabis for the purposes of treatment also sometimes use it to get high, to relax, to have fun. And the same goes for folks who are using cannabis in a recreational way; they might also be using it to cope with unpleasant emotions, or anxiety, or to help

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them sleep. So using these two terms creates a false sense of two dichotomous categories, when in fact the boundaries are messy. When talking with patients about their cannabis use, it's important to get a good picture of their reasons for use, the quantity and frequency of their use, and their preferred product's potency and active compound distribution (THC to CBD ratio) to help understand whether their cannabis use is problematic or risky. *(Editor's note: See the article "Currently Available Cannabis Products" in this issue to learn more about what products are on the market today.)*

CATR: Given how commonly cannabis is used, how should providers be on the lookout for CUD? Would you recommend universal screening for all patients in psychiatric treatment?

Dr. Walker: I recommend urine screening for all vulnerable populations: adolescents, pregnant women, patients with psychosis and other mental health problems. I don't see a downside to universal screening as long as there is sufficient time and resources. I would certainly recommend that all patients are at least asked about cannabis use. And for anyone using cannabis more than once a week, I would recommend a more detailed assessment for CUD.

"A common perception of cannabis is that you can't actually become addicted to it. We hear that all the time, even sometimes from medical professionals. But cannabis certainly can be addictive, and the research bears that out."

Denise Walker, PhD

CATR: How should we screen for CUD?

Dr. Walker: Start by asking, "How often and how much are you using?" Weekly use or more places a patient in a higher normative bracket that elevates the likelihood of CUD. Screening tools are often based on tests for alcohol use. There's a cannabis version of the Alcohol Use Disorders Identification Test (AUDIT) called the Cannabis Use Disorders Identification Test (CUDIT; www.tinyurl.com/yc3ujnkh). There is also the cannabis version of the Michigan Alcoholism Screening Test (MAST) called the Cannabis Abuse Screening Test (CAST; www.tinyurl.com/s5svdush). These screens are typically easy to use and can be quickly deployed in a busy clinical setting.

CATR: Let's shift the focus to cannabis withdrawal. What does it look like?

Dr. Walker: Cannabis withdrawal was added when the DSM went from version 4 to version 5 in 2013, so officially at least, it's a relatively new clinical entity. Symptoms usually start 24–48 hours after cessation of use. Cannabis withdrawal can last up to two weeks, so the time course is quite long. The intensity of symptoms is not as severe as something like alcohol or opioid withdrawal, though—it looks a lot like nicotine withdrawal. There is irritability, anger or aggression, loss of appetite, nervousness, insomnia, weird dreams, restlessness, and depressed mood. Physical symptoms can occur as well, like sweating, fever, chills, shakiness, tremors, and gastrointestinal discomfort. It looks very similar to acute anxiety, which can make differential diagnosis tricky.

CATR: How heavy of a user does someone have to be in order to develop a withdrawal syndrome?

Dr. Walker: That's not really known, and it probably varies by individual, so I can't give you a number of days of use or a specific quantity or frequency. But we do know that about 12%–17% of cannabis users have experienced withdrawal in the past year (Livne O et al, *Drug Alcohol Depend* 2019;195:170–177). It's quite common, so I don't think that only heavy daily users experience it, though rates of cannabis withdrawal certainly increase with heavier use. Among people who present for CUD treatment, 50%–75% of them endorse a history of withdrawal symptoms (Bahji A et al, *JAMA Netw Open* 2020;3(4):e202370). And it can be a big barrier to treatment. It's one of the main things that people point to when treatment is unsuccessful.

CATR: How is cannabis withdrawal treated?

Dr. Walker: First is to reassure the patient that withdrawal symptoms are not life-threatening. Often the treatment is just psychoeducation—"This is what to expect, this is the time course, this is what you could experience in the next week or two, and it will go away if you don't use." There doesn't need to be any type of specialized detox, just some good social support, good psychoeducation, and reassurance. I recommend that patients try to get plenty of sleep, take hot baths or showers, eat healthy food, get exercise—activities that might help address specific symptoms of withdrawal. Medications have been tried to treat withdrawal symptoms such as sleep disturbance. There has been interest in cannabinoid receptor agonists (dronabinol or nabiximols), and they do appear to reduce symptoms of withdrawal. If a patient reports that severe withdrawal symptoms have thwarted a CUD treatment attempt in the past, they might be good candidates for these medications, though they aren't used commonly.

CATR: And what treatments do we have to offer once a patient makes it through withdrawal?

Dr. Walker: While we do have treatments for CUD, the literature is not as robust as you might hope. CUD research really didn't start until the late 1980s, and research paradigms have been largely based upon those from alcohol research. The three treatment modalities with the most empirical support are cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), and contingency management (CM). For adolescents, you could add family therapy as well.

CATR: How can our readers learn more about the specifics of these therapies?

Dr. Walker: The principles employed in therapy for CUD are similar to treatment for other addictions or mental health conditions. But if readers are looking for specific resources, I would point them to a free online manual,

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developed for a multisite trial done in the late 1990s, that combines MET and CBT techniques (www.tinyurl.com/3bsdyaz8; Marijuana Treatment Project Research Group, *J Consult Clin Psychol* 2004;72(3):455–466). There are study manuals available for those working with adolescents as well. In fact, our group makes our manuals for MET available online (www.tinyurl.com/36r34psj).

CATR: And how do synthetic cannabinoids fit into all of this?

Dr. Walker: Synthetic cannabinoids are quite different; these are artificial drugs that act on the same brain receptors as THC, but they are different chemicals. These drugs evolve and change rapidly, making them difficult to test for. They are widely available, often sold at convenience stores or online. They bind to cannabinoid receptors, like natural cannabis, but the potency is much higher—they just overload the receptors. And the subjective experience of using them is pretty different than with natural cannabis. We see much higher rates of delusions and hallucinations, severe anxiety, and more physical symptoms such as racing heart, vomiting, and breathing problems. But synthetic cannabinoids are a relatively recent development that we just don't know much about. For example, even as a cannabis researcher, I didn't learn about them until 2008. I was conducting a military study for alcohol and our soldiers were talking about their use of "spice," which is a term for synthetic cannabinoids (Walker D et al, *Addict Behav* 2014;39(7):1139–1144). Nowadays they're also called "K2," "spike," and "fake weed." That seems to be one of the attractive aspects about synthetic cannabinoids: They are difficult to detect. They appeal to people being drug tested regularly, like military service members or those on probation or parole.

CATR: And did the subjects in your study who used synthetic cannabinoids develop use disorder and withdrawal?

Dr. Walker: Yes, absolutely. Again, the criteria for use disorder from substance to substance are essentially the same: continued use despite negative consequences. In the case of synthetic cannabinoids, the physical symptoms of intoxication and withdrawal were so much more intense than those produced by natural cannabis. In terms of treatment, we don't have much research done in the field. But I would recommend utilizing the same therapeutic techniques that have been shown to be effective for CUD and other SUDs as well: MET, CBT, and CM when possible.

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

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Currently Available Cannabis Products

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EM and Parker LA, *Adv Exp Med Biol* 2021;1264:1–13). Clinically, the focus remains on two specific elements: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the main psychoactive component, creating euphoria through its action on central cannabinoid-1 receptors. THC is also the component responsible for the majority of cannabis-associated adverse effects. CBD, on the other hand, has limited psychoactive effects, and evidence indicates that it is much safer than THC (Ford TC et al, *Curr Drug Abuse Rev* 2017;10(1):6–18).

Cannabis products

The majority of this article will focus on products that predominantly contain THC. But before we get there, we should acknowledge that there is a world of CBD products marketed for conditions as wide ranging as anxiety, hypertension, acne, and pain relief. Some products report the amount of CBD they contain; others don't. Many are combined with NSAIDs, menthol, melatonin, and other active agents. Patients must understand that although these products are widely available, their production methods and quality control are unregulated. They typically carry less risk than the high-THC formulations discussed below, but they lack rigorous safety testing and are not approved for the treatment of any psychiatric disorder.

Less common, though growing in popularity, are products containing delta-8 THC. This cannabinoid is structurally related to delta-9 THC and has similar though typically milder psychoactive effects. Delta-8 THC is not nearly as well studied as delta-9 THC and CBD, so we know relatively little about its risks. However, there are case reports of adverse effects including hypotension, breathing difficulties, and even coma, prompting the FDA to caution consumers against using these unregulated products (www.tinyurl.com/345xffy5). Since delta-8 is derived from low-THC strains of the hemp plant, it is not federally prohibited, though some states have banned its sale.

Strains

All cannabis products start with the cannabis plant, of which there are two main commercially available strains: sativa and indica. Your neighborhood "budtender" will tell you that these strains are not created equal. Anecdotally, sativa is said to give the user energy, causing laughter and giddiness, while indica is purported to have anxiolytic and analgesic effects, though this distinction is not backed by studies and is up for debate (Piomelli D and Russo EB, *Cannabis Cannabinoid Res* 2016;1(1):44–46). Countless hybrid varieties are sold as well, supposedly offering more nuanced, in-between experiences.

But regardless of strain, cannabis plants have become increasingly potent over time, as measured by percentage of THC. Today's cannabis averages about 20% THC, worlds away from the 1%–2% THC plants of the 1970s (Stuyt E, *Mo Med* 2018;115(6):482–486). Conversely, CBD levels have decreased,

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Currently Available Cannabis Products

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with some popular strains containing as little as 0.09% CBD. Importantly, the principal factor to consider when determining risk of adverse effects is THC content, not strain. Put simply, the higher the THC content, the more likely it is that the user will experience adverse effects.

Determining dose

When specified at all, cannabis concentration is typically reported as percentage of THC. In order to determine the amount of THC in a particular product, simply multiply the weight of cannabis by the THC percentage. To determine how much THC is winding up in the patient's body, multiply again by the bioavailability.

Bioavailability for inhaled THC is between 10% and 35%, while ingested THC is highly erratic (Grotenhermen F, *Clinical Pharmacokinetics* 2003;42(4):327–360). Cannabis products might be sold in ounces, while THC is usually discussed in terms of milligrams, so be sure to keep units consistent if you decide to undertake the calculation.

Let's work through a quick example. Your patient smokes daily. Over a week, they smoke an eighth of an ounce of whole-plant cannabis with 15% THC. How much total THC do they consume, and how much of it ends up in their serum each day?

To determine THC consumption:

1/8 oz = 3.54 g
3.54 g cannabis × 15% THC = 0.531 g THC

0.531 g THC ÷ 7 days/week = 0.076 g = 76 mg THC consumed daily

To determine how much THC makes it into the serum:

76 mg THC × 10%–35% bioavailability = Between 7.6 mg and 27 mg THC daily

People vary widely in their consumption patterns, but this example can be considered about average for a typical daily cannabis user (Sikorski C et al, *Subst Use Misuse* 2021;56(4):449–457).

Routes of administration

Inhalation

Inhalation remains the most common way to consume cannabis. When inhaled, THC rapidly enters the bloodstream and reaches the central nervous system (CNS) without the mediating effects of first-pass metabolism, producing psychoactive effects in seconds to minutes. Many cannabis inhalation products are available, all of which fall into one of three categories: 1) smoking, 2) vaporization, and 3) dabbing.

1. Smoking

There are many ways to smoke cannabis. Whole-plant cannabis, typically just the dried flowers and buds, can be smoked in a "joint" (plant material wrapped in paper) or a "blunt" (cannabis wrapped in tobacco). Both can be prepared at home or purchased pre-made. Pipes (homemade or purchased), bongs, bubblers, and hookahs are commonly used as well.

THC concentrates, also called "extracts" and containing upwards of 75% THC, can be consumed by smoking too. One form, "kief," is prepared by separating out THC-rich resinous glands, called trichomes, by using a grinder. Heating and pressing kief produces hashish or "hash." Both are usually mixed with whole-plant cannabis before consumption, either by smoking or vaporization.

2. Vaporization

Vaporization devices use lower temperatures than smoking, avoiding the formation of some combustion products. "Vaping" is therefore sometimes advertised as a healthier alternative to smoking whole-plant cannabis, though there is little evidence to support this claim. The most popular vaporizers are small handheld "vape pens" that allow on-the-go, discreet use of dried cannabis, oils, or concentrates. Flavorants can be added to enhance the experience. Larger tabletop vaporizers capable of generating huge volumes of inhalable vapor ("The Volcano" is one such popular device) are available as well. Vaping is especially popular among young people; in one study, up to one-third of young cannabis users (19 years and younger) reported vaping cannabis in the past 30 days (Wadsworth E et al, *Addict Behav* 2022;129:107258).

3. Dabbing

"Dabbing" is a process in which a "dab" of cannabis concentrate is placed in a "dab rig" (specialized glass device) and heated with a blowtorch, with the user inhaling the resulting volatilized chemicals. Dabbing involves very high temperatures, so users may inhale combustion products and impurities, risking acute lung and burn injuries—not to mention the occasional house fire.

The cannabis concentrate that comprises the dab is usually a form of butane hash oil (BHO), prepared by butane or alcohol extraction of THC from hashish. BHO comes in several forms with names like "budder," "shatter," "amber," and "honeycomb." All have a THC content of 80% or higher. The rapid volatilization of highly concentrated THC typically produces an intense, long-lasting effect, exposing the brain to high levels of THC.

Once a relatively niche activity, dabbing is becoming more mainstream. It is less studied than other forms of inhalation, but it seems to be on the rise among young people. One study reported an increased 30-day prevalence of dabbing among high school cannabis users from 28% in 2015 to 34.4% in 2017 (Tormohlen KN et al, *JAMA Pediatrics* 2019;173(10):988–989).

Oral ingestion

Compared to smoking, products taken orally must go through first-pass hepatic metabolism before reaching the CNS, delaying the onset of psychotropic effects for 30–90 minutes. Effects typically last longer but can be more unpredictable due to erratic GI absorption. This delay can lead some users to unintentionally take more than intended.

Edible cannabis products are no longer limited to the traditional "pot brownie." Today, cannabis oils and butters are infused into almost every edible product imaginable. Foods containing cannabis are marketed as a healthy, discreet, and paraphernalia-free alternative to smoking. Oral ingestion tends to be preferred by older consumers of cannabis for both medical and recreational use (Subbaraman MS and Kerr WC, *J Cannabis Res* 2021;3(1):17). In addition to food,

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Q&A With the Expert

Medicinal Cannabis

Deepak Cyril D'Souza, MD

Professor of Psychiatry, Yale University School of Medicine. Psychiatrist, VA Connecticut Healthcare System, New Haven, CT.

Dr. D'Souza, expert for this educational activity, has disclosed that he owns stocks in Jazz Pharmaceuticals and Biohaven Pharmaceuticals. Dr. Capurso has reviewed the content of this interview and determined that there is no commercial bias as a result of these financial relationships.

CATR: Can you tell us a little bit about your work in the field of cannabis?

Dr. D'Souza: For the past 25 years, I've been interested in the pharmacology of cannabis and cannabinoids. At first my interest was in relation to psychosis, but then it expanded to include the pathophysiology and treatment of cannabis use disorder (CUD). I have also been working with state legislators in Connecticut as they consider cannabis legislation, trying to inform them about the health consequences of cannabis, especially in young people.

CATR: Let's say a patient walks into your office and tells you they have a medical marijuana card. What does that mean?

Dr. D'Souza: The usual scenario starts when a patient goes to a physician who is certified within their state's medical marijuana program. The physician first must diagnose that patient with a condition that is approved for treatment with cannabis. Once the patient is certified, they can enroll in the state's medical marijuana program. After enrollment, they can then go to a state dispensary and purchase a cannabis product.

CATR: It seems strange that cannabis is illegal at the federal level, but is approved as a medicine and/or for recreational use in some states. How did we get here?

Dr. D'Souza: Yes, it's confusing. The federal government still sees cannabis and its principal active constituent—meaning delta-9-tetrahydrocannabinol (THC)—as a Schedule I substance. By definition, cannabis doesn't have a therapeutic use and has a high abuse liability. Some states have bypassed that by using a legal loophole. Technically, physicians are not prescribing marijuana, because that would be illegal. Instead, physicians are certifying patients for a condition that a state has decided qualifies for medical marijuana. And once certified, patients can then obtain medical marijuana through a state-sanctioned dispensary.

CATR: So it is up to states to decide which conditions qualify and which ones don't? This is different than other medications.

Dr. D'Souza: It's totally different. Other medications go through an approval process at the FDA, which is quite rigorous. The FDA standard typically requires two double-blind, randomized controlled trials with sample sizes of over 100 patients—sometimes thousands of patients. But cannabis approval gets around that, again due to various legal loopholes and technicalities. So, cannabis approval, whether it's medical or recreational, is decided by a state legislative body. The process differs from state to state, and the standard of evidence is overwhelmingly lower than that of the FDA. And keep in mind that each state has its own list of medical and psychiatric conditions for which medical cannabis is approved. There are various medical conditions on that list, and perhaps most relevant to your readers, a host of psychiatric conditions including autism, agitation, Alzheimer's disease, generalized anxiety, and PTSD. In addition, some states have given fairly broad latitude to certifying physicians: If the physician believes that cannabis will be helpful, then it can be prescribed. So, effectively, in those states there are no guidelines—it's left to the physician's discretion.

CATR: Could you summarize the current state of evidence for cannabis as a therapeutic agent?

Dr. D'Souza: I'll restrict my comments to psychiatric indications. My group reviewed this back in 2016 and concluded that there was very low-quality evidence to support the use of marijuana for any psychiatric condition (Wilkinson ST et al, *Annu Rev Med* 2016;67:453–466). A few other studies since then have come to essentially the same conclusion (Black N et al, *Lancet Psychiatry* 2019;6(12):995–1010). PTSD, which is perhaps the indication that has received the most attention, is a good example of the state of the field. There is one randomized controlled trial with THC (Bonn-Miller MO et al, *PLoS ONE* 2021;16(3):e0246990). Researchers took military veterans with PTSD and experience using cannabis and randomized them to receive high-dose THC, high-dose cannabidiol (CBD), a combination of the two, or placebo. They found no differences between the treatment groups *(Editor's note: See Research Update in this issue for more on this study).* There are several cohort studies as well that all show similar results. Other studies, some of which show some promise, are too underpowered to draw any definitive conclusions.

CATR: So we just don't know if cannabis works or not.

Dr. D'Souza: That's right. And we have to weigh the efficacy data, or lack of data, with the negative consequences of cannabis use. In sum, taking the very weak evidence for efficacy and robust knowledge of adverse effects, at the present time it's hard to justify recommending cannabis for any psychiatric disorder.

CATR: Would you say that cannabis is ever contraindicated?

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Dr. D'Souza: Cannabis and its derivatives can worsen the course of psychotic disorders, so people with an established psychotic disorder should avoid these substances. Furthermore, there is a concern that cannabis could precipitate a first episode of psychosis and trigger a chronic psychotic disorder in people who have a family history or who are clinically high risk. So these people shouldn't use cannabis either. I would apply that to bipolar disorder as well, especially those who become psychotic during mood episodes. Anxiety disorders are interesting—many people who use cannabis recreationally do so for its anxiolytic effects. But in some individuals, it can induce panic and anxiety. We see that in our laboratory studies; some subjects become very anxious and have panic attacks. It's been reported in the literature. So, cannabis can be a double-edged sword as it relates to anxiety. People with anxiety disorders might find cannabis anxiolytic initially, but once tolerance develops with regular use, they could experience significant withdrawal and rebound anxiety, which they then have to treat with larger doses, creating a vicious cycle (Connor JP et al, *Addiction* 2022;117(7):2075–2095). So, I would say people with anxiety disorders should also avoid it.

CATR: What about PTSD? Aren't there data to show that it can worsen outcomes?

Dr. D'Souza: There are some associational data, yes. Some colleagues looked at almost 50,000 veterans and found that those who used cannabis seemed to have worse PTSD outcomes (Wilkinson ST et al, *J Clin Psychiatry* 2015;76(9):1174–1180). So, PTSD patients should be advised to abstain from cannabis as well, until we have good-quality data showing beneficial effects.

CATR: Are there any other groups that should avoid cannabis in particular?

Dr. D'Souza: Young people should avoid cannabis—their developing brains are especially vulnerable to its effects. People with addictions to other substances should be cautioned that they are at an increased risk of developing CUD if they use cannabis.

CATR: You're painting a picture in which cannabis can be harmful to large groups of patients with little to no evidence of any mental health benefits. Yet state governments are saying that cannabis is safe, even beneficial. It sounds confusing.

Dr. D'Souza: It is very confusing, unfortunately. Explaining the difference between FDA and state approval and the lack of evidence for medical cannabis is sufficient for some patients. But others won't be convinced and will want to continue using it "medicinally." For me, the two most challenging groups are young people—an entire generation who have grown up with the concept of medical cannabis—and patients who have been using it for a long time already. They say, "See, we told you all along that it's OK." You won't convince many patients to change their use in one session; it has to be an ongoing conversation.

"With patients who want to continue using cannabis 'medicinally,' I explore the negative consequences of use, and what benefits there might be if they quit or cut back. Maybe it's that they're spending too much money, or they don't want to do it in front of their kids."

Deepak Cyril D'Souza, MD

CATR: What tips do you have for those conversations?

Dr. D'Souza: Explore the negative consequences of use for each patient, and what benefits there might be for them if they quit or cut back. Maybe it's that they're spending too much money. Other reasons are "I don't want to do this in front of my kids" or "I want to apply for a certain job but I don't think I'm going to pass a workplace drug test." Sometimes it comes down to another person in the patient's life: "My spouse is frustrated that our vacation plans are limited because I can't travel without my cannabis." Some of my patients with psychotic disorders tell me cannabis improves their psychotic symptoms, even though the details of their situation clearly show that is not the case. Usually, over time I'm able to point out to them that every time their use of cannabis increases, they end up in the hospital. Sometimes it takes several hospitalizations to solidify the connection. Or with bipolar patients, they get manic when they increase their use, and maybe it takes one or two times for them to see the link.

CATR: What about patients who are adamant that their use carries no negative consequences?

Dr. D'Souza: Sometimes it takes a bit of exploration to find the consequences that exist. For young people, I might ask, "Tell me about your pattern of cannabis use." They might say, "Thursdays, Fridays, Saturdays, and Sundays. I don't smoke on Mondays, Tuesdays, and Wednesdays." When I ask why, they say, "I have classes." And they'll begrudgingly concede that when they smoke, they don't have the motivation to study or they forget what they're learning. For a middle-aged adult who absolutely insists they don't have any negative consequences, I might ask, "Would you be OK with your teenage son or daughter smoking cannabis?" Then the conversation takes a different tone. They'll say, "Actually I'm not so sure about that..." And that leads to an opportunity to discuss why.

CATR: Sounds like motivational interviewing.

Dr. D'Souza: You're right. My approach is not deliberately motivational interviewing, but I guess it developed in that direction. *(Editor's note: See* Addiction Report, *March/April 2021 for more on motivational interviewing.)*

CATR: And what if patients continue to use anyway, saying that they enjoy cannabis? How do you discuss cannabis use with your patients within a framework of harm reduction?

Dr. D'Souza: I definitely have patients who will continue to use, despite my best efforts. The key here is THC content—that is what drives addiction. I would prefer that if patients are going to use cannabis, they use forms with

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Expert Interview – Medicinal Cannabis

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high CBD or at least a low THC:CBD ratio. In fact, my colleagues in the UK have suggested that the government should make low-THC/high-CBD cannabis legally available in order to cut down on the use of recently developed forms of cannabis with very high THC content like shatter, dab, or some vaping products with 80% or 90% THC. Before the 1990s, typical THC content was around 4%.

CATR: Given how rapidly things are changing, how do you recommend that clinicians stay up to date on this topic?

Dr. D'Souza: One great resource is an organization called Systematically Testing the Evidence on Marijuana (STEM), which is a collaboration between the Department of Veterans Affairs and the University of Oregon (www.cannabisevidence.org). They have brief summaries on specific topics that are continually updated as new information comes forth. Each summary is easily digestible and takes only a few minutes to read but provides links to the primary literature. In terms of legislation, clinicians should familiarize themselves with the website of their state's public health department. To my knowledge, most states have a website detailing approved indications for cannabis, patient and provider eligibility, etc. Finally, I think that clinicians should really be paying attention not just to legalization, but to commercialization. Alcohol and tobacco have been around for centuries, but the game changer for both was the commercialization of those products. Likewise, the commercialization of cannabis is going to be a huge part of how our patients perceive, access, and use it. An environment in which companies are selling cannabis for profit is very different from allowing people to grow a few plants in their backyard for home consumption.

CATR: Thank you for your time, Dr. D'Souza.

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Currently Available Cannabis Products

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drinks are starting to include cannabis as well. Alcoholic and non-alcoholic beverages containing cannabis are gaining popularity and are starting to be manufactured by larger beverage companies (www.tinyurl.com/2hkfwdju).

While edibles have largely been unregulated, some states are starting to increase labeling requirements quantifying THC content and defining portion sizes. Dosing charts with graded recommendations are sometimes attached to wrappings and posted in stores, with 5 mg starting to emerge as a "standard dose." The hope is that increased labeling will improve the predictability of the psychoactive effects caused by edibles, though whether this turns out to be the case remains to be seen, especially considering the wide range of bioavailability.

Sublingual

Like inhalation, cannabis that is taken sublingually bypasses first-pass metabolism. As a result, effects are typically felt within a minute or two. Tinctures, liquids prepared through alcoholic extraction of cannabis, are available in varying concentrations. They are sold in dropper bottles with plastic applicators and tend to be favored by those using cannabis for medicinal purposes. Oil-based sprays, which typically contain flavoring, can be used sublingually and buccally.

Other routes

Cannabis-infused topicals, lotions, balms, and patches are applied directly to the skin for transdermal delivery. These products don't cause any appreciable psychoactive effects and are advertised mainly for localized relief of pain and inflammation. Transdermal delivery of cannabis products is more efficient for CBD than THC due to differences in skin permeability (Grotenhermen, 2003).

Suppositories are available for vaginal and rectal use, typically to provide relief of painful menstruation and abdominal and pelvic pain syndromes, though they're not widely used.

CATR VERDICT: Cannabis is available in a dizzying array of products. As the prevalence of these products continues to rise, so too will the understanding of their relative harms and risks. Until then, maintain a working knowledge of what is available so that you can engage in informed discussion with your patients.

Carlat Publishing News

Updates on some additional resources we're working on:

The Carlat Psychiatry Report: The September issue explores college mental health; upcoming topics include psychotherapy in psychiatric practice as well as depression.

The Carlat Hospital Psychiatry Report: Current issues cover minimizing the use of restraints and paraphilic disorders.

The Carlat Geriatric Psychiatry Report: The current issue covers late-life depression; upcoming topics include bipolar disorder as well as substance use in older adults.

The Carlat Child Psychiatry Report: The current issue covers catatonia and sensory processing disorders. Upcoming topics include developmental trauma disorder and use of legally available substances in children and adolescents.

Research Updates

PTSD

Can Smoking Marijuana Reduce PTSD Symptoms?

Gregory Lande, DO. Dr. Lande, author of this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Bonn-Miller MO et al, *PLoS ONE* 2021;16(3):e0246990
STUDY TYPE: Randomized controlled trial

More and more veterans are using cannabis to treat their PTSD symptoms, despite the lack of high-quality safety and efficacy data and the high comorbidity between PTSD and cannabis use disorder (Bryan JL et al, *J Subst Abuse Treat* 2021;122:108254). Researchers hoped to fill this knowledge gap by utilizing a double-blind crossover design to assess three preparations of smoked cannabis for the treatment of PTSD.

The study was conducted in two stages. In Stage 1, which lasted three weeks, 80 veterans with PTSD were randomized into four groups: high THC (12% THC), high CBD (11% CBD), THC+CBD (7.9% THC and 8.1% CBD), and placebo (<0.03% THC and <0.01% CBD). For context, a recent nationwide study of cannabis dispensaries found that THC and CBD content in cannabis products can vary widely. Among smoked cannabis products from medical dispensaries, the average THC content was 19.3% (range 0%–35%) and the average CBD content was 2.0% (range <5%–40%) (Cash MC et al, *PLoS ONE* 2020;15(3):e1230167).

Participants received 37.8 grams of the relevant study drug with no restrictions on frequency of use. The primary outcome, change in PTSD severity, was measured with the Clinician-Administered PTSD Scale (CAPS-5). At the end of Stage 1, all four groups demonstrated an overall reduction in symptoms ranging from 8.5 to 15.2 points out of a possible 80; however, the amount of symptom reduction was not significantly different between any of the groups.

In Stage 2, the remaining participants (n=74) were re-randomized into one of three active treatment groups: high THC, high CBD, and THC+CBD. This allowed for both within-subject and between-subject comparisons. All groups again experienced symptom reduction, but this time one difference reached statistical significance: The THC+CBD group had greater symptom reduction compared to the high CBD group (16.4 vs 5.7). Adverse events (AEs) throughout were characterized as mild to moderate and were similar across placebo treatment groups. A total of 13 participants discontinued the study due to an AE. Three AEs had >10% frequency: cough (12.3%), throat irritation (11.7%), and anxiety (10.4%).

The researchers behind this study acknowledged several limitations, the most significant being the fact that few participants were cannabis naïve. In fact, participants were asked to abstain from cannabis for two weeks prior to enrolling in the trial, and many were in cannabis withdrawal by the time the study started, possibly skewing results (ie, reporting improved symptoms due to alleviation of withdrawal rather than PTSD symptoms). Patient expectation likely affected the results as well, suggested by the fact that effect sizes across all groups—even placebo—were much larger than typical PTSD medication trials.

CARLAT TAKE
Despite the hint of a signal in one treatment group, this study fails to convincingly demonstrate that cannabis is an effective treatment for PTSD. The trial's modest size and methodological shortcomings mean that further study is still warranted, but at the moment, we would discourage the use of cannabis as a PTSD treatment.

OUD

Sublocade vs SL Buprenorphine After Release From Jail

Peter J. Farago, MD. Dr. Farago, author of this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Lee JD et al, *JAMA Netw Open* 2021;4(9):e2123032
STUDY TYPE: Randomized comparative effectiveness trial

When people with opioid use disorder (OUD) are released from incarceration, they have a high risk of overdose—especially if they are not prescribed any medication for OUD. We know that methadone, sublingual buprenorphine/naloxone (SL-Bup), and injectable naltrexone all improve OUD outcomes in this population, but what about the relatively new long-acting injectable buprenorphine (XR-Bup, brand name Sublocade)? In this new study, researchers compared SL-Bup with XR-Bup to assess feasibility of administration and acceptability among people being released from incarceration.

Researchers enrolled 52 incarcerated, soon-to-be-released adults from New York City prisons who were already receiving SL-Bup for OUD. Half were randomized to start XR-Bup in prison with the goal of continuing it in the community. The other participants remained on SL-Bup. All participants were followed for eight weeks post-release. The primary clinical outcome was treatment retention.

The researchers first examined whether it was even feasible to give XR-Bup injections in incarceration settings. They concluded that it was. Most participants (21 of 26) received at least one dose of the medication before release (mean number of doses 2.3). Those on the injection required fewer daily jail clinic visits and had no incidents of diversion (whereas there were two incidents in the SL-Bup group). This led researchers to conclude that starting XR-Bup while incarcerated saves both time and labor.

Several post-release clinical outcomes were also superior in the XR-Bup group as compared to the SL-Bup group. There was a two-fold increase in buprenorphine treatment retention at week eight (69% vs 35%). The average length of time that patients stayed on buprenorphine after release was higher if they were receiving XR-Bup (6.1 weeks vs 2.6 weeks). There were more opioid-free urine tests in the XR-Bup group as

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compared to the SL-Bup group (55.4% vs 38.5%). No differences in the rates of serious adverse events were observed between the two groups, and no overdoses were observed in study participants.

The researchers did identify a few barriers to XR-Bup, including lack of knowledge about the formulation, perceived lack of access in the community, opposition to needle sticks, and a preference for staying with the familiar SL formulation. At the conclusion of the study, seven XR-Bup participants chose to switch back to SL-Bup, citing injection pain and preference.

CARLAT TAKE

Although these findings are preliminary, and it will likely be some time before it is widely available in prison settings, XR-Bup appears to be a promising intervention for an extremely high-risk population. Expanding access to XR-Bup in the general outpatient setting will also be a critical step in making this intervention feasible.

GAMBLING

Internet-Based Approaches for Gambling Issues

Amy Ton, MD, and Deepti Anbarasan, MD. Dr. Ton and Dr. Anbarasan, authors of this educational activity, have no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Sagoe D et al, *J Behav Addict* 2021;10(3):546–565

STUDY TYPE: Systematic review and meta-analysis of randomized sham-controlled trials

Problematic gambling is common, affecting up to 6.5% of all adults. But only 10% of them get treated, at least in part due to limited provider availability and stigma. The easy access and anonymity offered by internet-based gambling programs address both barriers. But how well do they work?

Researchers conducted a systematic review and meta-analysis, compiling 13 randomized trials that enrolled over 2,000 participants. Eight of the studies had control groups, the specifics of which varied between trials. Overall, 22 treatments were tested; 13 of them were based on cognitive behavioral therapy (CBT), while the others were based on a range of other psychotherapeutic interventions (motivational interviewing, couples therapy, and brief advice, among others). The number of sessions ranged from one to 28 (mean 9.9 sessions), and four of the protocols included therapist support. The outcomes were gambling frequency, amount of money lost, and score on a gambling severity scale (different studies used different scales), which the authors called general gambling symptoms.

Results showed that internet-based treatments were associated with improved outcomes, particularly for general gambling symptoms. At the conclusion of treatment, the effect size (Hedge's g) for improvement of general gambling symptoms was 0.729, indicating a medium to large effect. The effect sizes for gambling frequency and amount of money lost were more modest (0.291 and 0.190, respectively). Ten of the studies included assessments after a follow-up period (ranging from one to 36 months, mean 8.3 months), and these showed that benefits persisted over time; effect sizes for general gambling symptoms, gambling frequency, and amount of money lost at follow-up were g=1.197, g=0.361, and g=0.202, respectively. The effect sizes being higher at follow-up than at the conclusion of treatment is a statistical consequence of the fact that not all studies included follow-up periods.

Patients with more severe symptoms tended to show a greater degree of improvement, and interventions that included therapist support were associated with greater benefit. Unsurprisingly, studies that included a control group typically had smaller effect sizes. The authors compared these results with previous findings and determined that internet-based treatments did not work quite as well as in-person therapy but did work better than self-guided interventions (Goslar M et al, *J Behav Addict* 2017;6(2):142–162).

CARLAT TAKE

This meta-analysis suggests that internet-based treatments for problematic gambling may be helpful. Consider seeking them out, especially if your patient prefers virtual treatment or if face-to-face counseling is unavailable.

CBT

Computer-Based Training for CBT for Women in Residential Treatments

Kristyn Lao, MD, and Deepti Anbarasan, MD. Dr. Lao and Dr. Anbarasan, authors of this educational activity, have no relevant financial relationship(s) with ineligible companies to disclose.

REVIEW OF: Kelpin SS et al, *J Subst Abuse Treat* 2022;132:108622

STUDY TYPE: Randomized open-label controlled trial

Cognitive behavioral therapy (CBT) is helpful for substance use disorders, and studies have shown that computer-based CBT is effective in outpatient settings. But is computer-based CBT also effective in intensive residential treatment settings? Researchers sought to answer this question by investigating the efficacy of an adjunctive CBT program called Computer-Based Training for Cognitive Behavioral Therapy (CBT4CBT).

This pilot study took place in a residential treatment program for women with addiction that offered medication management, individual and group counseling, and case management services. Sixty-three women were randomized to one of two groups. One group (n=29) continued in the standard residential treatment program, which consisted of individual and group therapy, medications, and case management. The other group (n=34) participated in adjunctive CBT4CBT. Participants were predominantly Black (79.4%), with an average age of 41.2 years (range 18–65 years). Most identified opioids (61.9%) and cocaine (73.0%) as their primary substance use problem, and nearly half (47.6%) identified using both.

The CBT4CBT program consists of seven videos (30–45 minutes each), interactive exercises, and "homework" to be completed between sessions for extra skills practice. Women accessed the program on tablets in a private on-site area for a minimum of two sessions per week for 3.5 weeks. These sessions were in addition

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CE/CME Post-Test

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

1. How can you determine the amount of THC in a patient's blood serum (LO #1)?
   [ ] a. Multiply the mass of cannabis by the THC percentage, then divide by the bioavailability
   [ ] b. Divide the mass of cannabis by the THC percentage, then multiply by the bioavailability
   [ ] c. Multiply the mass of cannabis by the THC percentage, then multiply by the bioavailability
   [ ] d. Divide the mass of cannabis by the THC percentage, then divide by the bioavailability

2. According to Dr. Walker, approximately what percentage of individuals who use cannabis develop cannabis use disorder (LO #2)?
   [ ] a. 5% [ ] b. 17% [ ] c. 30% [ ] d. 50%

3. According to Dr. D'Souza, what are the standard requirements for physicians to be able to prescribe medical cannabis (LO #3)?
   [ ] a. Registration with a federal cannabis treatment program
   [ ] b. Completion of a Risk Evaluation and Mitigation Strategy
   [ ] c. Physicians are not allowed to prescribe cannabis
   [ ] d. No standard requirements

4. According to a 2021 study of adults with gambling issues, how did internet-based treatments fare in addressing participants' general gambling symptoms (LO #4)?
   [ ] a. Improved general gambling symptoms, with a small effect size
   [ ] b. Improved general gambling symptoms, with a medium to large effect size
   [ ] c. Were partially associated with a worsening of general gambling symptoms
   [ ] d. Did not separate from placebo

5. What is the onset of action for cannabis ingested orally (LO #1)?
   [ ] a. 2–3 minutes [ ] b. 10–30 minutes [ ] c. 30–90 minutes [ ] d. 90–120 minutes

6. According to Dr. Walker, why are synthetic cannabinoids attractive to some people (LO #2)?
   [ ] a. They cause lower rates of anxiety and hallucinations
   [ ] b. They have a lower potency
   [ ] c. They are difficult to detect during drug tests
   [ ] d. There is ample clinical evidence for their use in treatment

7. According to Dr. D'Souza, what did a 2015 observational study conclude about the effects of cannabis on 50,000 veterans with PTSD (LO #3)?
   [ ] a. Cannabis was associated with worsened symptoms of PTSD
   [ ] b. Cannabis was associated with improved symptoms of PTSD
   [ ] c. Cannabis had no effect on PTSD outcomes
   [ ] d. The evidence was inconclusive

8. What did a 2021 randomized controlled trial conclude about the effects of cannabis on individuals with PTSD (LO #4)?
   [ ] a. A high dose of THC improved PTSD symptoms compared to placebo
   [ ] b. A high dose of CBD improved PTSD symptoms compared to placebo
   [ ] c. The combination of a high dose of THC and CBD improved PTSD symptoms compared to placebo
   [ ] d. There was no statistically significant difference between the treatments and placebo

Research Updates

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to the services offered in the residential treatment program.

Researchers assessed drug and alcohol use with urine toxicology and breathalyzer, as well as self-report. Participants were assessed at the study's initiation, at the time of facility discharge, and at four and 12 weeks post-discharge. At 12 weeks post-discharge, women in the CBT4CBT group had lower relapse rates (30.4% vs 47.6%) and reported fewer substance use days (3.4 vs 9.2) of their primary problematic substance. Time to relapse was also about a week longer in the CBT4CBT group (57.4 days vs 51.8 days). Because the study did not enroll enough patients, it was not powered to detect statistical significance, but the trends were in favor of CBT.

CARLAT TAKE

Computer-based CBT programs have already shown promise as an adjunctive treatment for outpatients, and this small pilot demonstrates that CBT4CBT seems to be helpful in residential settings as well. This study only evaluated efficacy as an adjunctive treatment, so more robustly controlled trials are needed before we can give this program a full recommendation. Nonetheless, its relatively low cost and ease of access make it something to consider adding to usual treatment.

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In Brief: Gabapentin

It's been five years since reports first emerged that gabapentin could increase the risk of fatal overdose in those using illicit opioids. Though usually safe on its own, gabapentin potentiates opioid effects, including respiratory suppression. Now a recent CDC report shows that the problem is getting worse as gabapentin prescriptions skyrocket (www.tinyurl.com/mtjhhfkd). Between 2019 and 2020, gabapentin was detected in nearly 10% of postmortem toxicology testing of those who died from opioid overdose. Moreover, the number of overdose deaths in which gabapentin was detected doubled from the first quarter of 2019 to the second quarter of 2020. Educate patients about the risks of mixing gabapentin with opioids, and exercise caution when considering gabapentin for any patient with opioid use disorder.

—Noah Capurso, MD. Editor-in-Chief of
The Carlat Addiction Treatment Report

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