THE CARLAT REPORT
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IN THIS ISSUE

Focus of the Month:
Addiction in Pregnancy

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

1. Identify the negative outcomes of substance use during pregnancy and/or lactation on the fetus or infant.
2. List the key points for naloxone prescribing and use.
3. Summarize some of the findings in the literature regarding addiction treatment.

Breastfeeding and Addiction

Pochu Ho, MD. Assistant Professor of Psychiatry, Yale University. Director of Psychiatric Consultation Service, West Haven VA Medical Center, CT.

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

Addiction providers typically treat one patient at a time. But once we start working with a patient who is breastfeeding, that number jumps to two (or more in the case of twins, triplets, etc). Although breastfeeding has a host of infant health benefits, many providers do not feel confident managing patients who are nursing. In order to deliver the best care to these patients, providers need to be aware of how substances find their way into breast milk, how to discuss commonly misused substances, and which medications are safe to prescribe.

Highlights From This Issue

Pregnancy changes the way clinicians should think about the manifestations of substance use disorders and how to treat them.

Naloxone prescribing is an important harm reduction tool that saves lives, but knowing how your patients can access naloxone and understanding relevant regulations is crucial.

Addictive substances and medications alike can find their way into the breast milk of lactating women; however, the effect these substances have on breastfeeding babies can vary.

Bioavailability in breast milk
Properties of substances
Substances are transferred into breast milk by diffusion down a concentration gradient, with many variables determining

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Q&A With the Expert

The Pregnant Patient With Substance Use Disorder

Ariadna Forray, MD

Associate Professor of Psychiatry, Yale School of Medicine, New Haven, CT. Interim Chief, Section of Psychological Medicine. Director, Center for Wellbeing of Women and Mothers, Yale New Haven Hospital.

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

CATR: Could you tell us what your role is and what you do?
Dr. Forray: I'm an associate professor of psychiatry at Yale and I do research on treatments for pregnant and postpartum patients with substance use disorders (SUDs). Clinically, I'm the interim chief of the Section of Psychological Medicine at Yale New Haven Hospital and work with patients in our adult sickle cell clinic.
CATR: Can you give our readers an understanding of the scope of addiction in pregnancy?
Dr. Forray: The majority of substance use in pregnancy is with legal substances. Anywhere from 8% to 10% of pregnant patients use alcohol, and a similar percentage use cigarettes. About 6% use some illicit substance, predominantly cannabis, followed by cocaine, heroin, and

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amphetamines. Around 2.5% use prescription opioids (www.datafiles.samhsa.gov). Use of hypnotics, psychedelics, and inhalants is much lower. We lack data on what proportion of these patients have diagnosable SUDs, but I would venture to guess that it would match the non-pregnant population of reproductive-age patients.

CATR: Another area in which we lack data is how shame and stigma might prevent pregnant patients from receiving adequate care. How should practitioners handle this issue?

Dr. Forray: There are anecdotal reports that pregnant patients feel shamed by providers when seeking treatment, particularly medications for opioid use disorder (MOUDs). In fact, proper MOUD treatment during pregnancy is shockingly low (Tiako MJN et al, *Obstet Gynecol* 2021;137(4):687–694). Patients feel that providers are thinking, "Why are you using? You're harming your baby." But remember, 99.9% of pregnant patients want to do what's right for their pregnancy. That's why patients are coming to you; they are overcoming a lot of shame and they're very vulnerable. It's important to mindfully set aside any personal bias or preconceived notions before the interview.

CATR: How do you recommend we do this?

Dr. Forray: Ask yourself: "Where is this patient right now, where do they want to go, and how can I help them get there?" During the encounter itself, try to positively frame the interaction and do not shy away from directly acknowledging the patient's difficulties. It lays the foundation for a strong therapeutic rapport that the patient can make use of later on as you hopefully continue to work together. I always say something like, "I can tell that it was very hard for you to come here today. Thank you for trusting me and being open because I can see that this is very difficult for you."

CATR: Let's talk about alcohol use in pregnancy. Fetal alcohol syndrome (FAS) is well known, but there are other teratogenic effects that providers should be aware of and need to counsel their patients about.

Dr. Forray: That's right. FAS is the most well known and is the leading cause of a nongenetic developmental delay, but the full syndrome is relatively rare. However, fetal alcohol effects lie along a spectrum, and it's much more common that children suffer a less severe, but still significant, neurodevelopmental disorder with behavioral issues and cognitive delays. This milder syndrome is less studied and less well known, so patients may think that a little drinking is OK, when really it might still confer risk for these fetal alcohol effects.

CATR: And how do you recommend that providers address these effects with patients, given how common alcohol use is?

Dr. Forray: A lot of reproductive-age patients, who might not have an alcohol use disorder, still binge drink. To give you some background, about 45% of pregnancies in the US are unplanned. For patients with an SUD, it's 60% to 90%, and many don't find out that they're pregnant until late in their first trimester, which is already past the critical period of exposure to alcohol. So it is very important for providers to consider birth control for reproductive-age patients who binge drink.

CATR: There is a sense in the community that the recommendation for abstinence from alcohol during pregnancy is overblown. What should we tell a patient who hears or reads that it is actually OK for them to drink moderately?

Dr. Forray: Well, there is no time in pregnancy when it's safe to drink; there simply is no amount of alcohol that has been shown to be safe. While critical organ formation occurs early in pregnancy, the brain continues to develop throughout pregnancy and beyond. A recent paper found that even light to moderate prenatal alcohol exposure was associated with increased psychopathology, attention deficits, and impulsivity compared to unexposed children (Lees B et al, *Am J Psychiatry* 2020;177(11):1060–1072). So the recommendation remains that there is no safe amount and no safe time for alcohol use in pregnancy. It's also important to emphasize that the type of alcohol doesn't matter

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either. Beer is no safer than wine, which is no safer than liquor; it is the overall amount of alcohol consumed that counts.

CATR: And what if the patient continues to drink even after pregnancy has been confirmed?

Dr. Forray: None of the medications that we typically use for alcohol use disorder, such as naltrexone or acamprosate, have been studied for efficacy in pregnancy. That being said, naltrexone appears to at least be safe and has been studied for efficacy in opioid use disorder (OUD) during pregnancy (Wachman EM et al, *Clin Ther* 2019;41(9):1681–1689). So naltrexone is a potential option, along with evidence-based psychotherapies such as motivational interviewing, cognitive behavioral therapy, or mutual help groups such as AA. I would avoid disulfiram altogether given the physiological stress a disulfiram-alcohol reaction might put on the fetus.

CATR: Many prescribers, especially those without expertise, can be hesitant to prescribe to pregnant patients. What kind of safety issues exist for medications prescribed for SUDs?

Dr. Forray: Other than for opioids, we don't have studies that evaluate the efficacy of most medications for addiction in pregnancy. In fact, the safety profile of many of these medications is, in a way, a secondary issue, because we don't know if they work in pregnancy at all.

CATR: There are substantial data for OUD treatments.

Dr. Forray: Yes, that's right. For decades, the only medication for OUD was methadone, and that was the gold standard. Methadone is not known to lead to any congenital malformations and is effective; it reduces cravings, prevents use of other illicit substances, decreases risky behavior, enhances prenatal care, and enhances nutrition (Mozurkewich EL and Rayburn WF, *Obstet Gynecol Clin North Am* 2014;41(2):241–253). In 2010, there was a sentinel paper by Hendrée Jones, called the MOTHER study, which compared methadone and buprenorphine with the primary outcome of neonatal opioid withdrawal syndrome (NOWS). NOWS, formerly known as neonatal abstinence syndrome, manifests with babies being jittery, more difficult to console, and having difficulty feeding (Jones HE et al, *N Engl J Med* 2010;363(24):2320–2331). If not treated, babies can develop seizures. That paper caused a paradigm shift and brought buprenorphine to the forefront of MOUD in pregnancy because it showed that, relative to methadone, buprenorphine decreased the length of stay, decreased the amount of morphine infants required, and decreased the duration of NOWS. Since then, either methadone or buprenorphine are acceptable MOUDs in pregnancy.

"Although fetal alcohol syndrome (FAS) is the most well known, the full syndrome is relatively rare. Fetal alcohol effects lie along a spectrum, and it's much more common that children suffer a less severe, but still significant, neurodevelopmental disorder with behavioral issues and cognitive delays. So patients may think that a little drinking is OK, when really it might still confer risk for these fetal alcohol effects."

Ariadna Forray, MD

CATR: Let's say a pregnant woman presents to your office seeking MOUDs. What is the proper way to start her on methadone or buprenorphine?

Dr. Forray: In non-pregnant patients, methadone is almost always started in a methadone clinic. But during pregnancy, it is often started on an obstetrical floor, where mental health clinicians with little experience prescribing methadone might be asked to weigh in as a psychiatric consultant. Luckily, it's pretty straightforward. Just like in non-pregnant patients, the initial starting dose for methadone is anywhere between 10 and 30 mg, depending on how much they are using at baseline. I rarely give the 10 mg dose unless the patient is using small amounts of opioids, because you really want to avoid opioid withdrawal during pregnancy. Two to four hours after the initial dose, you reassess with the Clinical Opiate Withdrawal Scale (COWS). Re-dose with another 5–10 mg of methadone if the COWS is 8 or above. Reassess in another 2–4 hours, re-dose if the COWS is greater than 8 again, and simply repeat for the first 24 hours. After 24 hours, calculate the dose that they've received, and that becomes their daily maintenance dose. Given that adjustments are typically made every 3–5 days, most patients can transition to outpatient follow-up on this dose without requiring any further adjustment.

CATR: And what about buprenorphine?

Dr. Forray: Ideally, outpatient buprenorphine induction should be reserved for a pregnancy of less than 24 weeks gestation. If there is any medical comorbidity, or greater than 24 weeks gestation, it's best to start buprenorphine inpatient due to risks to the fetus during opioid withdrawal. In pregnancy, you want to start buprenorphine at a COWS of 8 with a dose of 2 or 4 mg. If the COWS is 10 or above, I favor the 4 mg dose. From there, the protocol is the same as with methadone.

CATR: Is it necessary for prescribers to stick to the monoproduct buprenorphine (Subutex) instead of the co-formulated buprenorphine/naloxone (Suboxone)?

Dr. Forray: Traditionally, the recommendation had been for buprenorphine alone (Subutex). More recently, as we have gathered data on the safety of buprenorphine/naloxone, we have moved away from that strict

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recommendation. The inclusion of naloxone does not seem to have any negative impacts in pregnancy (Jumah NA et al, *BMJ Open* 2016;6(10):e011774; Nguyen L et al, *Am J Addict* 2018;27(2):92–96). In fact, some providers prefer to prescribe buprenorphine/naloxone if they have a particular concern for diversion.

CATR: You mentioned the importance of avoiding withdrawal.

Dr. Forray: Yes. Opioid withdrawal causes a catecholamine surge, which leads to increased uterine contractions and decreased placental blood flow. At the same time there is fetal motor hyperactivity, leading to increased oxygen demands. This creates a dangerous mismatch that can lead to fetal demise. For that reason, I am very aggressive in keeping pregnant patients out of withdrawal. The stakes are much higher than just physical discomfort.

CATR: What dose adjustments might be required as pregnancy progresses?

Dr. Forray: Usually patients will need higher doses as pregnancy progresses due to increased volume of distribution and changes in hepatic metabolism. Patients in the late second or third trimester metabolize methadone and buprenorphine much more quickly, so they should receive split dosing to maintain a steady state. Some may require doses that are higher than you'd normally expect: frequently 100–120 mg of methadone, or higher.

CATR: What about tapering after delivery?

Dr. Forray: There's no consensus on how to do it. I recommend switching to once-a-day dosing soon after delivery. There is obviously a significant volume of distribution shift right away, but a lot of other physiologic changes take time, so for the first 2 weeks I will only decrease the dose slightly and taper more aggressively afterwards. Since there is no standardized protocol, doses should be adjusted according to the clinical picture. Let the signs and symptoms of the patient guide the taper. Cravings mean the dose is too low, for example, and sedation means the dose is too high.

CATR: Let's talk about smoking in pregnancy. What should clinicians know?

Dr. Forray: Tobacco is one of the most common substances used in pregnancy. We did a prospective study and found that 96% of patients who drank alcohol were able to stop, and around 70% of patients who used cannabis or cocaine were able to stop during pregnancy. But only 32% who smoked managed to achieve abstinence (Forray A et al, *Drug Alcohol Depend* 2015;150:147–155). Smoking also is associated with a host of poor outcomes. Preterm delivery, ectopic pregnancy, placental abruption, fetal growth restriction, and placenta previa—all are increased with smoking. Postpartum smoke exposure increases the risk of sudden infant death syndrome threefold, and long-term impacts include cognitive effects, attention deficits, and even an increased risk of schizophrenia (Quinn PD et al, *JAMA Psychiatry* 2017;74(6):589–596). Unfortunately, we don't have any good treatments for it other than contingency management, behavioral interventions, and behavioral counseling. Nicotine replacement, varenicline, and bupropion haven't been adequately evaluated to make recommendations one way or another.

CATR: What about stimulants?

Dr. Forray: Stimulants are the worst class of drugs when it comes to pregnancy outcomes because they are powerful vasoconstrictors and disrupt placental function and placental blood flow. Like smoking, there are risks of preterm delivery, placental abruption, low birth weight, and placenta previa, but the risk is even higher with stimulants. Long-term developmental effects, hyperactivity, and behavioral dysregulation are seen as well, though the epidemic of "crack babies" that people worried about in the late 1980s and early 1990s did not quite come to pass.

CATR: The prevalence of cannabis and vaping has increased drastically in recent years. What is known about the effects of these on pregnancy?

Dr. Forray: There is much less tar content in vaping, which is a good thing, but we don't know whether any of the other constituents are harmful, so I never explicitly recommend vaping, even as a tool to quit smoking. In terms of cannabis, risk of preterm birth, low birth weight, and placental abruption are present but less than for tobacco or stimulants. Developmental delays seem to be directly related to the amount of THC consumed. So a harm reduction strategy for patients who simply cannot abstain from using cannabis is to recommend using products with lower THC content.

CATR: What are some resources that providers can utilize when treating pregnant patients?

Dr. Forray: Reprotox is a really good specialist website with the latest evidence for medications during pregnancy and lactation, including commonly prescribed psychotropics (www.reprotox.org). And don't underestimate the power of Micromedex, which has a pregnancy and lactation section for all its medication listings (www.micromedexsolutions.com). In fact, providers who have institutional access to Micromedex also will have access to Reprotox. Other resources include the American Society of Addiction Medicine (ASAM) website, which has useful guidance for treating pregnant patients (www.asam.org). The CDC also has some fantastic resources under their reproductive health section (www.cdc.gov/reproductivehealth/maternalinfanthealth/substance-abuse/substance-abuse-during-pregnancy.htm). Finally, the Providers Clinical Support System (PCSS), which is a national training and clinical mentoring project, has online courses for providers specifically interested in learning more about MOUDs in pregnancy (www.pcssnow.org/education-training/training-courses/treating-women-for-opioid-use-disorder-during-pregnancy-clinical-challenges/).

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

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Breastfeeding and Addiction

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how much ultimately makes it from high concentration (plasma) to low concentration (milk). The journey begins at ingestion, with the drug's bioavailability determining how much of it is absorbed into the plasma. Once absorbed, drugs with high molecular weight, and those that are protein bound, will tend to stay in the plasma. Drugs that are lipid soluble or have a high pKa (more basic) will concentrate in the milk. In fact, drugs that are basic and lipid soluble can achieve an even higher concentration in the milk than in the plasma (D'Apolito K, *Clin Obstet Gynecol* 2013;56(1):202–211). We describe the properties of specific substances later in this article.

Maternal factors

Renal and hepatic impairment may slow down drug elimination, causing drugs to accumulate in the body and, in turn, become more likely to be excreted into milk. Illicitly purchased drugs are often adulterated, and therefore mixtures of substances can find their way into breast milk, even if the patient has supposedly used only one drug.

Infant factors

Infants and young children, particularly those with certain underlying medical issues, are more vulnerable to the effects of drugs than their adult counterparts. Drug clearance gradually increases with age, from 5% in infants 24 weeks old to 100% by 68 weeks, or 1 year and 4 months of age (D'Apolito, 2013). Therefore, expect drug effects to be magnified in infants less than a year old.

Substances and breastfeeding

Alcohol

The most commonly misused substance by patients who are breastfeeding in the US, by far, is alcohol: up to 50% in studies. Because alcohol has a low molecular weight, is not protein bound, and is basic, its level in breast milk parallels that in plasma. The alcohol level in milk peaks 30–60 minutes after maternal consumption, then falls rapidly. While the American Academy of Pediatrics (AAP) recommends complete abstinence during breastfeeding, most experts say nursing is safe as long as less than 8 ounces of wine or 2 beers are consumed at a sitting and 2 hours have elapsed before breastfeeding or pumping (Reece-Stremtan S and Marinelli KA, *Breastfeed Med* 2015;10(3):135–141).

Opioids

Other substances are a different story entirely. Heroin has low protein binding and high lipid solubility. As expected, it readily crosses into breast milk. Adulteration of heroin is quite common, with fentanyl, and analogues such as carfentanyl, being the most problematic. The risk of oversedation and overdose for infants breastfeeding from patients using heroin, and particularly heroin adulterated with fentanyl, is high. The American College of Obstetricians and Gynecologists (ACOG) does not recommend breastfeeding for patients using heroin (Committee on Obstetric Practice and Breastfeeding Expert Work Group. Breastfeeding challenges. ACOG; 2021). One prescription medication to be especially wary of is codeine. Just like heroin, it is a prodrug that is rapidly metabolized into morphine. High levels of morphine can be found in the breast milk of patients taking codeine, and codeine can be found in many medications, such as analgesics and cough syrups.

Cocaine

Cocaine is particularly prone to accumulation in breast milk. In fact, the concentration of cocaine in breast milk is 8 times higher than in plasma. Cocaine has a bioavailability of 80%–90% as well as a high lipid solubility, which is why it accumulates in the breast milk so efficiently (Bartholomew ML and Lee MJ, *Contemporary OB/GYN* 2019;64(9):22–26). The CDC and the AAP therefore recommend total abstinence from cocaine while breastfeeding.

Cannabis

Like cocaine, tetrahydrocannabinol (THC) also has levels in breast milk 8 times that of maternal plasma (Reece-Stremtan and Marinelli, 2015). As one of the primary psychoactive components of cannabis, patients who are breastfeeding should avoid using cannabis products. Studies have shown that the feces of infants contains THC metabolites, indicating that THC is not only consumed by infants through breast milk, but also absorbed and metabolized in their bodies. It is important to keep in mind that marijuana has become increasingly potent in recent years, potentially making the amount of THC in breast milk even higher than just several years ago.

Tobacco

Many patients are able to abstain from smoking, or at least cut back, during pregnancy. However, up to 50% resume their prior pattern of cigarette use postpartum (Reece-Stremtan and Marinelli, 2015). Nicotine and other agents in cigarettes are readily transferred to breast milk, and secondhand smoke exposure contributes to respiratory issues and sudden infant death syndrome. Therefore, we should encourage smoking cessation in all parents with newborns, whether they are breastfeeding or not.

Medications for addiction and breastfeeding

While substance misuse should generally be avoided during breastfeeding, some medications that are commonly prescribed for addictive disorders are safe to prescribe while nursing. Both methadone and buprenorphine are lipid-soluble weak bases, but have a relatively high molecular weight and are protein bound. Therefore, these drugs only cross into breast milk in small amounts (D'Apolito, 2013). Breastfeeding is not only safe but encouraged in patients who take methadone and buprenorphine because the small amount of drug that finds its way into breast milk is safe and decreases the severity of neonatal opioid withdrawal syndrome (Committee on Obstetric Practice and Breastfeeding Expert Work Group, 2021).

In terms of medication for alcohol use disorder (AUD), disulfiram passes into breast milk and therefore is not recommended for breastfeeding (Fenner S. Safety in lactation: Alcohol dependence. National Health Services; 2020). Human data for acamprosate are lacking, so there is no recommendation for its use one way or another. In contrast, naltrexone is only minimally excreted into breast milk, and its use can therefore be continued.

Gabapentin and topiramate do not

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have FDA approval for AUD but are commonly used off label for this indication. Gabapentin's excretion into breast milk is minimal, and infant blood levels of topiramate are less than one-fifth of the maternal blood level. Although this implies that these drugs should be safe to prescribe, they have not been rigorously investigated in this context, so there are no firm guidelines regarding breastfeeding (Graves L et al, *J Obstet Gynaecol Can* 2020;42(9):1158–1173.e1). Evidence for the safety of bupropion and varenicline is similarly lacking. Nicotine replacements are safer alternatives to cigarette smoking.

Psychotropic medications and breastfeeding

The use of psychotropic medications is common in patients with addictions. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are safe during breastfeeding. Due to teratogenicity, carbamazepine and valproate are generally avoided during pregnancy. In contrast, these medications can be resumed or started during breastfeeding. Lithium is safe during breastfeeding, but pediatricians should check a blood level periodically or if the baby ever gets dehydrated, typically from a GI illness.

Antipsychotics are found in low levels in breast milk, but the potential for extrapyramidal symptoms in infants is remote. Therefore, patients who need antipsychotics can take them and continue breastfeeding. Benzodiazepines can cause sedation and physiological dependence in infants, so although not completely contraindicated, low-dose and shorter-acting agents should be favored (Payne JL, *Med Clin North Am* 2019;103(4):629–650). For a summary of drugs and medications during breastfeeding, see the table at left.

Impact of Drugs and Medication While Breastfeeding

Avoid During Breastfeeding	
Alcohol[1]	Disulfiram
Benzodiazepines[1]	Illicit opioids
Cocaine	THC
Codeine	Tobacco
Not Enough Data for Recommendation	
Acamprosate	Topiramate
Gabapentin	
Permitted in Breastfeeding	
Antipsychotics	Naltrexone
Buprenorphine	Nicotine replacement
Carbamazepine[2]	SNRIs
Lithium[2]	SSRIs
Methadone	Valproic acid[2]

[1]Not totally contraindicated but requires caution; see text for further recommendations
[2]Check infant plasma levels

CATR VERDICT: Patients who misuse substances on a regular basis should not breastfeed. In contrast, patients who have been on methadone or buprenorphine during pregnancy can continue these medications during lactation. For AUD, prescribe naltrexone but not disulfiram. Most psychotropics are safe during breastfeeding.

Q&A With the Expert

Naloxone Prescribing

Phillip Coffin, MD

Director of Substance Use Research, San Francisco Department of Public Health, San Francisco, CA.

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

CATR: Welcome, Dr. Coffin. Tell us what you do.

Dr. Coffin: I'm a physician boarded in addiction medicine, infectious disease, and internal medicine. I am the director of substance use research at the San Francisco Department of Public Health, and on faculty at UCSF. My research is mainly in substance use, and I have various projects dealing with treatments for stimulant and alcohol use disorders, as well as HIV and hepatitis C prevention. A large focus of my work has been the development of opioid overdose prevention programming.

CATR: Which patients should be receiving naloxone prescriptions?

Dr. Coffin: We should think about prescribing naloxone to three broad patient groups. The first and most important group is people using drugs purchased outside of the health care industry: that is to say, anybody using drugs purchased on the street.

CATR: You recommend prescribing naloxone to people using any street drugs, not just those who use opioids?

Dr. Coffin: Fentanyl is changing the way we think about overdose prevention. It is taking over the illicit drug supply and is often being sold as something else. Someone who uses only cocaine has a reasonable chance of inadvertently exposing themselves to fentanyl. I should also mention that fentanyl is increasingly being smoked instead of injected. In general, opioid overdose is uncommon when not injecting; however, fentanyl seems to be different. People who smoke or sniff fentanyl, some of whom have never injected, are now experiencing overdoses. That is why we recommend prescribing naloxone to anyone who uses any street drugs—they're the same people who are most likely to be present when an overdose happens.

CATR: What is the second group that should have access to naloxone?

Dr. Coffin: The second group is a subset of patients who have been prescribed opioid analgesics, as set forth in the 2016 CDC guidelines (Dowell D et al, *MMWR Recomm Rep* 2016;65(1):1–49). This includes anyone prescribed opioids at a dose

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of 50 milligram morphine equivalents (MME) or greater, anyone taking benzodiazepines along with opioids, anyone with a history of a substance use disorder or opioid overdose, and anyone with medical comorbidities that increase overdose risk. The guidelines are complicated, but basically, anyone who is prescribed opioids in any significant amount or who has additional risk factors should get naloxone.

CATR: And the third group?

Dr. Coffin: The third group is people who are likely to witness an opioid overdose. This includes parents, friends, and roommates. We call this "third-party prescribing," and while it's not universally authorized, most states allow for it. There are far too many stories out there about a family member finding their loved one who just overdosed, calling the ambulance, and simply having to wait too long for it to arrive. Third-party prescribing allows for a life-saving intervention without reliance on the immediate availability of health care professionals.

CATR: What forms of naloxone are available? What are their advantages and disadvantages?

Dr. Coffin: The IM injection is the most basic, consisting of a vial and a syringe—just like those used by patients to self-administer insulin years ago. Some patients may be hesitant using needles, but people who use drugs by injection will likely be comfortable with them. An advantage of the IM is that you know exactly how much naloxone the patient is getting, and it acts almost immediately. There is an auto-injector, which is a self-contained device that delivers naloxone with a needle. It's a fantastic device. It talks to you and walks you through naloxone administration in real time. The needle is robust and will go through a pair of jeans, but the cost is unwieldy for most settings and I believe it is no longer being produced.

CATR: And then there is the ubiquitous nasal spray.

Dr. Coffin: The nasal spray is the most commonly prescribed because it's very easy to administer, but it is important to be aware that people can have quite different absorption through the nasal mucosa. The dose for the nasal spray is 10 times higher than the IM injection in order to account for this difference, and that means people who absorb the medication readily will get a pretty steep dose of naloxone. Some recipients of the nasal spray therefore report headaches, which isn't typically seen with other forms of naloxone. Interestingly, we see headaches with the buprenorphine/naloxone co-formulated product (brand name Suboxone) in around 10%–15% of patients, but very few headaches in patients taking buprenorphine alone (brand name Subutex). Given that the nasal spray is easy to administer, reliable, and widely available, it is usually the preferred formulation for prescribing naloxone. *(Editor's note: See News of Note on page 9 for more information about a new high-dosage naloxone formulation, KLOXXADO.)*

"The most important thing to do when you're prescribing naloxone is to make sure that patients let those around them know where the naloxone is located. This holds for third-party prescribing as well; you want to make sure that everyone in the household knows where the naloxone is kept and that it is easily accessible."

Phillip Coffin, MD

CATR: I've heard concern from patients and providers alike that nasal congestion might interfere with the effective delivery of naloxone when given intranasally. Are there any data behind that?

Dr. Coffin: I don't believe so. The IM injection is generally 0.4 mg, and that dose works reliably even in the setting of fentanyl. The nasal spray is 4 mg, which is approximately bioequivalent to 2 mg of IM. So even if full absorption doesn't occur, the nasal spray should be more than sufficient to revive an overdose victim. I'm not particularly concerned about nasal congestion or anatomical abnormalities.

CATR: And what do these different formulations cost?

Dr. Coffin: The nasal spray cost, while not trivial, is covered by many insurance plans and is within reach of some people paying out of pocket. The brand-name Narcan is around $150 per two-pack; a generic has been approved but is not yet available. I'd love to see the price go down, but given the manufacturing costs, I don't think it's possible to get it under $30. The auto-injector has recently gone out of production (though there is still some backlog availability) but it was always priced high, anywhere from several hundred to several thousand dollars. The IM injection is the most economical; with contracts, it's inexpensive enough to be distributed by many naloxone distribution programs. The IM injection is rarely prescribed on an individual basis, with the exception of some Medicare Part D plans that don't cover the nasal spray.

CATR: Can you tell us what you mean by naloxone distribution programs?

Dr. Coffin: There are two models of getting naloxone into the hands of those who need it. One is prescription, which is what most of us in the medical system are used to. The other is distribution, in which an organization purchases naloxone in bulk and gives it out to large numbers of patients. The most common setting for this model is syringe exchange programs; these organizations are able to get naloxone cheaply enough that they can hand out thousands of doses to the people who are around overdoses all the time. Individual prescribing is important, but the distribution model is the real harm reduction workhorse; most overdose reversals in the community come from naloxone obtained through the distribution model, namely via a standing order.

CATR: And can you explain what a standing order is?

Dr. Coffin: Essentially, a standing order allows a physician to write a naloxone order in such a way that the medication can be dispensed under their license to a large group of people, without the physician needing to directly see individual patients and write individual scripts. Naloxone is not a controlled substance, so most states have passed standing order laws of some kind, with the exception of Idaho, Nebraska, and Oregon (SAFEProject, 2021). This is important information to communicate to

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Expert Interview—Naloxone Prescribing
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patients who can't or don't want to see a prescriber.

CATR: Where does a standing order allow naloxone to be dispensed from?

Dr. Coffin: A standing order is generally used to allow naloxone to be dispensed from a place like a syringe exchange or a pharmacy. For example, I issue the standing order for the Drug Overdose Prevention and Education Project in San Francisco, and the naloxone finds its way to the staff at the syringe exchange programs, who then dispense it directly to the clients. This is not billed through insurance; it is done outside of what we think of as the traditional health care system.

CATR: So should providers refer their patients to needle exchange programs or have them go to their local pharmacy to get naloxone?

Dr. Coffin: If you are a prescriber seeing a patient who warrants a naloxone prescription, I generally recommend just prescribing it to the patient. But you can also take steps to make sure people in the community know that naloxone is widely available. You can list the places that dispense naloxone so clients know they can ask for it, or you can put a flyer in the waiting room for people who don't want to talk to you about their substance use.

CATR: What about patients who aren't injecting drugs and who do not go to syringe exchange programs? How might they find where naloxone is available under these standing orders?

Dr. Coffin: Accessing naloxone can be a little bit trickier for these patients, and that's part of the reason it's important to prescribe naloxone directly to patients whenever you can. Some states have great web-based resources for naloxone as well, which will typically list pharmacies in the area that have standing orders. SAFEProject, which stands for Stop the Addiction Fatality Epidemic, has an online compilation of state-specific information with links to each state's online resources (www.safeproject.us/naloxone-awareness-project/state-rules/). Another resource is a summary of state naloxone access laws put out by the Legislative Analysis and Public Policy Association (www.legislativeanalysis.org/wp-content/uploads/2020/10/Naloxone-summary-of-state-laws-FINAL-9.25.2020.pdf).

CATR: Naloxone is unusual in that, unlike other medications, patients do not typically administer it to themselves. Providers therefore have to educate patients on how to use naloxone and make them into naloxone educators themselves. Can you give us some specific language to use with patients?

Dr. Coffin: Sure. First, consider the term "overdose"; we use it all the time, but it can be problematic. Many people, especially those taking prescription opioids, only think of an overdose as an intentional act—like swallowing a whole bottle of pills. They don't think of the term as simply having too much opioid in your body at a given moment. So instead of using the word "overdose," I'll explain naloxone like this: "Opioids can cause a bad reaction where you stop breathing, and that can be fatal. Naloxone is a medication that can reverse that." In fact, we interviewed patients prescribed opioids and found that almost half of those who had overdosed denied having an "overdose," but described a "bad reaction" where they couldn't be woken up without assistance such as being revived by paramedics (Behar E et al, *Ann Fam Med* 2016;14(5):431–436).

CATR: What are other key points that you emphasize when prescribing naloxone?

Dr. Coffin: The most important thing to do when you're prescribing naloxone is to make sure that patients let those around them know where the naloxone is located. This holds for third-party prescribing as well; you want to make sure that everyone in the household knows where the naloxone is kept and that it is easily accessible. The nasal spray and auto-injector don't need much instruction in terms of use. But be sure to explain to your patient that if they see somebody not breathing, they should administer naloxone right away, call 911, and attempt whatever type of resuscitation they are comfortable providing—such as rescue breathing or chest compressions. It's not complicated, but all the pieces need to be there. The Substance Abuse and Mental Health Services Administration, commonly called SAMHSA, has a free downloadable resource called Opioid Overdose Prevention Toolkit that lays out how to recognize and respond to an overdose (www.store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742).

CATR: What are some important risk factors for opioid overdose?

Dr. Coffin: There are two main modifiable risk factors that practitioners can easily focus on. The first is consumption of other drugs, particularly depressants like alcohol and benzodiazepines. The other is tolerance, which can be lost in as little as 3 days of abstinence. Some patients taking buprenorphine might stop the medication in order to use opioid agonists, and those few days are enough to have a loss of tolerance. More commonly, people being released from prison and leaving abstinence-based treatment programs have sky-high mortality for the first 48 hours. Patients being tapered off opioids also lose tolerance toward the end of the taper.

CATR: How should clinicians stay up to date regarding federal and local regulations, both pertaining to opioid use disorder treatments in general and to naloxone specifically?

Dr. Coffin: Again, many regulations are state specific, but I would recommend that anyone treating patients with opioid use disorder be aware of a few local laws that are on the books in most states. First, multiple states now have co-prescribing mandates that require a naloxone prescription for patients who are receiving opioids or who have certain risk factors. Most, but not all, states have third-party prescription laws and standing order protocols. There are also Good Samaritan laws that give some protection against low-level drug violations for people who report an overdose. That said, these laws are complex; no one can realistically keep track of all of them. I recommend a website through Temple University called LawAtlas (www.lawatlas.org), which maintains a registry of laws relevant to the psychiatric practitioner. They have a section devoted to naloxone prescribing (www.pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139).

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

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News of Note

A New High-Dose Naloxone: Life Saver or Punishment?

The FDA approved a new intranasal formulation of naloxone on April 30, 2021. Called KLOXXADO, this formulation distinguishes itself from other delivery systems by its higher dose, with each nasal spray containing 8 mg of naloxone. In comparison, the most widely used naloxone product, Narcan Nasal Spray, contains 4 mg of naloxone.

What's the rationale behind this higher-dose formulation? Recall that intranasal naloxone is used to quickly reverse opioid overdoses. The most common scenario is that someone who has used heroin or fentanyl passes out, and one of their friends (who may use drugs themselves) or family members finds them and must take quick action to save the person's life. Assuming they have a vial of naloxone, the bystander sprays a dose into the overdose victim's nostril and waits 2–3 minutes for a response—and may have to readminister in the other nostril if the victim remains obtunded. The idea behind KLOXXADO is that doubling the first dose of naloxone is more likely to revive the victim on the first try, preventing a potentially fatal delay. Hikma, the manufacturer of KLOXXADO, claims the need for multiple doses is becoming more common due to the abundance of fentanyl and fentanyl derivatives in the illicit opioid supply.

FDA approval was granted based on the results of two pharmacokinetic studies in which healthy volunteers received naloxone intramuscularly, intravenously, or via KLOXXADO, then had their plasma concentrations of naloxone measured over time. Naloxone is readily absorbed through the nasal mucosa, so it was no surprise that it was detectable just a few minutes after a dose of KLOXXADO. Naloxone is also effective at overdose reversal when given intramuscularly, and the studies showed both KLOXXADO and intramuscular doses reached their maximum concentrations at the same time point (about 15 minutes).

Approval was not granted based on efficacy data, but we know naloxone is safe and effective at reversing opioid overdoses, so we can be confident KLOXXADO will be safe and effective as well. However, some harm reduction experts dispute that fentanyl overdoses inherently require more naloxone to reverse than overdoses caused by other opioid agonists. In fact, some data indirectly suggest that fentanyl overdoses might not require any more naloxone than heroin overdoses (Bell A et al, *Subst Abus* 2019;40(1):52–55).

If these experts are right, KLOXXADO might be designed to deliver an unnecessarily high dose of naloxone, and this is likely to worsen the discomfort of those having their overdoses reversed. A double dose of naloxone means twice as many antagonist molecules are suddenly available to displace the opioid agonist from mu receptors, increasing risk and severity of precipitated withdrawal. Some worry that people who use opioids might see this harsher withdrawal as punitive, and that this could discourage users from acquiring naloxone rescue kits in the first place.

CATR'S TAKE

Without firm evidence of its necessity—not to mention its likely high price tag—consider KLOXXADO only for patients who have received multiple naloxone doses in the past. Far more important than the number of milligrams per spray is that patients who use opioids have naloxone on hand, regardless of the particular formulation.

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

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Research Updates

THERAPY

Does CBT Enhance Pharmacotherapy for Addiction?

REVIEW OF: Ray LA et al, *JAMA Network Open* 2020;3(6):e208279

Does cognitive behavioral therapy (CBT) provide any extra benefit when added to medication treatment for substance use disorders? It's not clear. Most notably, in the COMBINE study of comparative treatments for alcohol use disorder (see *CATR*, Nov/Dec 2019), a combined behavioral intervention (that included CBT) added to medical management did not improve outcomes. And yet, in real-world practice, CBT continues to be widely offered. Recognizing this evidence gap in common practice and clinical guidelines, Ray et al did a systematic review and meta-analysis of combined CBT and pharmacotherapy for various substance use disorders.

The researchers searched over 10,000 abstracts to identify 30 studies meeting their inclusion criteria: peer-reviewed, English-language RCTs involving adults receiving either individual or group CBT in addition to medication. Trials mostly included alcohol, cocaine, and opioid use disorders, and medications trialed included naltrexone, disulfiram, nefazodone, desipramine, methadone, buprenorphine, acamprosate, and levodopa. The results were grouped according to three main questions, and an estimate of effect size was reported using Hedges' g (0.2 small, 0.5 medium, 0.8 large).

The researchers found that CBT plus medications was somewhat superior to usual care interventions plus medications. These "usual care interventions" included basic medication clinic add-ons like clinical management, drug counseling, and group counseling. CBT was better than these basic interventions at reducing both the frequency (g = 0.18) and quantity (g = 0.28) of substance use.

That was the good news for CBT. The bad news was that CBT was not more effective than other specific forms of therapy (eg, motivational enhancement therapy, 12-step facilitation, contingency management [g = 0.05]) and did

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not demonstrate benefit when included as an add-on to medical management, such as in the COMBINE trial (g = 0.06–0.17).

CATR'S TAKE

This review shows that CBT is at best modestly effective when started alongside medications but not superior to other forms of psychotherapy or when added to medical management. However, before souring on CBT, it's important to note that this meta-analysis tried to combine many studies of different disorders and medications with varying efficacy. While we wait for more data that match CBT with specific medications for specific substance use disorders, it is reasonable to offer CBT given its low risk and some likelihood that it may build capacity for recovery.

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

OUD

Starting Buprenorphine: Is Timing Everything?

REVIEW OF: Jakubowski A et al, *J Subst Abuse Treat* 2020;119:108140

Buprenorphine is a safe and effective treatment of opioid use disorder (OUD), but studies show that less than two-thirds of patients treated with buprenorphine are still in treatment 6 months later (Timko C et al, *J Addict Dis* 2016;35(1):22–35). Since the highest rate of dropout is during the first month of treatment, Jakubowski and colleagues decided to look at factors affecting dropout and hypothesized that the timing of the first dose of buprenorphine might be a decisive factor. The researchers speculated that patients receiving their first dose on their very first visit might be more likely to stay in treatment over time.

The investigators looked retrospectively at a cohort of 222 patients engaged in treatment in a federally qualified health center who were treated with buprenorphine. They divided them into two groups: those who were prescribed buprenorphine at the initial evaluation, and those who were prescribed buprenorphine later but within 30 days of the initial visit. Treatment consisted of buprenorphine prescription plus visits with a primary care physician every 1–2 weeks until stable, then monthly.

Of the 222 patients, 89 (40%) were prescribed buprenorphine at the initial visit, and 133 patients (60%) were prescribed buprenorphine later but within the first 30 days. Eighty percent of patients remained in treatment through the first 30 days. A higher percentage (85% vs 77%) of same-day prescription receipt patients remained in treatment through the first 30 days, but this increase was not statistically significant (p = 0.11). It was noted that alcohol or benzodiazepine use was associated with delayed prescription of buprenorphine, but the results were the same even when these factors were adjusted out.

CATR'S TAKE

This retrospective study did not identify a statistically significant improvement in treatment retention associated with initiating buprenorphine on the first day of evaluation when compared with later initiation. On the other hand, early treatment did not show any sign of increasing dropout, and it should be emphasized as it may decrease overdose risk and be associated with other unmeasured benefits.

—John O'Neal, MD. Dr. O'Neal has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

COCAINE

Cannabidiol for Crack-Cocaine Craving: Negative Findings

REVIEW OF: de Meneses-Gaya C et al, *Braz J Psychiatry* 2020 (Epub ahead of print)

Cocaine use disorder is notoriously difficult to treat, with no approved pharmacological treatments. Brazil, where this study was done, is said to have one of the highest cocaine consumption rates in the world (Abdalla RR et al, *Addict Behav* 2014;39(1):297–301), and use of crack-cocaine is disproportionately common, with a one-year prevalence of 2% compared to 0.3% in the US (www.tinyurl.com/asy9ajtj). Prior studies have suggested that cannabinoids may help reduce cocaine craving and consumption, but none of these studies tested pure cannabidiol (CBD) or specifically examined people who use crack-cocaine. The authors designed a randomized, double-blind, placebo-controlled trial of cannabidiol to treat acute craving, anxiety, and depression during withdrawal from crack-cocaine.

The subjects were 31 adult male inpatients with DSM-IV diagnoses of crack-cocaine dependence who were admitted to a psychiatric hospital. Most used at least 5 times a week, and the mean duration of use was 12 years. The subjects were randomly assigned to a treatment group that received 150 mg of CBD twice daily for 10 days, or a control group that received placebo.

Each day, researchers tried to induce cocaine craving by showing participants brief films filled with crack-related content. The level of craving was assessed before and after each showing, using validated scales. Symptoms such as depression, anxiety, and insomnia were assessed as well using the Beck Depression Inventory and Beck Anxiety Inventory.

The completion rate was high: 79% in the treatment group and 82% in the control group. Both groups showed significant improvement over the course of the trial in intensity of craving and saw improvements in anxiety and depression; however, there were no differences on any measure between the active and control groups.

Limitations of the study include the small number of participants, the short trial period, and the relatively low dose of CBD. Importantly, the inpatient setting with its enforced abstinence may have washed out any additional effects of CBD.

CATR'S TAKE

CBD was no more helpful than placebo for diminishing cocaine cravings in this admittedly small and rather limited research trial, despite promising results from preclinical studies. Hopefully, larger and more flexibly dosed studies will provide more definitive data in the future.

—David Moltz, MD. Dr. Moltz has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.
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These questions are intended as a study guide. Please complete the test online at www.carlataddictiontreatment.com. Learning objectives are listed on page 1.

1. Which of the following medications should be avoided during breastfeeding (LO #1)?
   [ ] a. Methadone [ ] b. Lithium [ ] c. Naltrexone [ ] d. Disulfiram
2. The two main modifiable risk factors for opioid overdose are opioid tolerance and the consumption of other drugs, especially depressants (LO #2).
   [ ] a. True [ ] b. False
3. In a 2020 study of OUD, how did same-day buprenorphine initiation versus delayed buprenorphine initiation affect likelihood of remaining in treatment after 30 days (LO #3)?
   [ ] a. A lower percentage of same-day patients remained in treatment, but the difference was not statistically significant
   [ ] b. A significantly lower percentage of same-day patients remained in treatment
   [ ] c. A higher percentage of same-day patients remained in treatment, but the difference was not statistically significant
   [ ] d. A significantly higher percentage of same-day patients remained in treatment
4. Studies have shown that THC and cocaine levels in breast milk can reach up to 8 times that of maternal blood. What chemical properties cause drugs to concentrate in breast milk (LO #1)?
   [ ] a. Drugs that are lipid soluble with a high molecular weight
   [ ] b. Drugs that are protein bound in the plasma and basic
   [ ] c. Drugs that are lipid soluble and basic
   [ ] d. Drugs that are water soluble with a high molecular weight
5. In a recent study of opioid overdose, what percentage of patients who overdosed reported having a "bad reaction" to their prescribed opioids rather than having an "overdose" (LO #2)?
   [ ] a. 15% [ ] b. 25% [ ] c. 50% [ ] d. 75%
6. How does CBT compare to other therapies as an add-on to medical management for patients with SUD (LO #3)?
   [ ] a. CBT was more effective than motivational enhancement therapy, but was not more effective than contingency management
   [ ] b. CBT was equivalent to other forms of therapy
   [ ] c. CBT was more effective than all of the other specific forms of therapy
   [ ] d. CBT was equally as effective as 12-step facilitation and was more effective than all of the other specific forms of therapy
7. In the MOTHER study, buprenorphine decreased the length of stay, the amount of morphine infants required, and the duration of neonatal opioid withdrawal syndrome (NOWS), compared to methadone (LO #1).
   [ ] a. True [ ] b. False
8. According to Dr. Coffin, a standing order allows prescribers to do which of the following (LO #2)?
   [ ] a. Write a naloxone order that is dispensed to a large group of people without the physician needing to directly see each patient
   [ ] b. Write a buprenorphine order that is dispensed to a large group of people without the physician needing to directly see each patient
   [ ] c. Write an order that allows patients to refill medications indefinitely
   [ ] d. Write a naloxone order that is dispensed to people who are unable to afford the prescription

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CANNABIS

Nicotine Patch for Cannabis Withdrawal?

REVIEW OF: Gilbert DG et al, *Psychopharmacology (Berl)* 2020;237(5):1507–1519

As more and more states legalize marijuana and the prevalence of cannabis use increases, more people will be experiencing cannabis withdrawal symptoms, which are difficult to treat. The authors of this study hypothesized that the degree of negative affect experienced in cannabis withdrawal would be mitigated by nicotine. They designed a randomized, blinded, placebo-controlled trial to test the hypothesis.

Investigators recruited 101 people with moderate cannabis use disorder between the ages of 18 and 35. Participants were paid to stop using cannabis for 2 weeks (abstinence verified by

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urine tetrahydrocannabinol [THC] levels). They were then split into two groups, with one group receiving a 7 mg nicotine patch (n = 51) and the other receiving a placebo patch (n = 50). Physical symptoms of cannabis withdrawal (such as restlessness, sleep difficulty, decreased appetite or weight loss, abdominal discomfort or nausea, tremor, or headache) and negative affect were measured every other day for 15 days using the Profile of Mood States scale (POMS).

The results showed that the nicotine patch was more effective than placebo in reducing negative affect associated with cannabis withdrawal after 7 days (Cohen's d = 0.2). Perhaps most interestingly, the results applied to all patients, whether they were tobacco users or not. Disappointingly, nicotine patches did not reduce overall withdrawal symptoms, and in fact increased nausea, probably an effect of the nicotine. The authors note that use of a higher-strength patch might have improved the results.

CATR'S TAKE

Nicotine can attenuate symptoms of negative affect during cannabis withdrawal, but not primary withdrawal symptoms. The study didn't evaluate whether nicotine helps maintain cannabis abstinence. As a clinician, you can try this fairly harmless approach for cannabis-addicted patients who already use nicotine, but don't expect miracles.

—John O'Neal, MD. Dr. O'Neal has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.