THE CARLAT REPORT
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CURRENT COVERAGE OF TOPICS IN ADDICTION MEDICINE

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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Psychedelic Treatment of Addiction

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

1. Identify strategies for treating opioid use disorder in pregnant patients.
2. Understand the risks and benefits of psychedelic treatment of psychiatric and addictive disorders.
3. List the pros and cons of various buprenorphine induction strategies.
4. Summarize some of the findings in the literature regarding addiction treatment.

Treating Opioid Use Disorder During Pregnancy

Ariadna Forray, MD. Associate Professor of Psychiatry; Chief of Psychological Medicine Section, Psychiatry; Director, Center for Wellbeing of Women and Mothers; Yale Medical Director, ACCESS Mental Health for Moms, New Haven, CT.

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

Opioid use during pregnancy has skyrocketed over the past decade with opioid use disorder (OUD) diagnoses at childbirth more than doubling from 2010 to 2017 (Hirai AH et al, *JAMA* 2021;325:146–155). Untreated OUD is associated with a host of negative outcomes for both parent and child, though many of these can be mitigated with medications for opioid use disorder (MOUD), namely methadone and buprenorphine. However, pharmacokinetic shifts that occur during pregnancy affect how these medications should be prescribed. Here, we'll review the evidence supporting MOUD during pregnancy and get into the nuts and bolts of how to properly prescribe them.

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Highlights From This Issue

Feature Q&A
Psychedelics represent a new frontier in the treatment of psychiatric and addictive disorders.

Q&A on page 6
Ketamine and esketamine are medications with impressive rapid antidepressant effects, but they have misuse potential and must be managed carefully.

Article on page 8
Novel buprenorphine induction strategies are being developed for patients with opioid use disorder. Many hold promise, but the tried-and-true standard induction protocol still has an edge.

Q&A With the Expert

Psychedelics and Addiction
Snehal Bhatt, MD

Chief, Addiction Psychiatry; Professor, Psychiatry and Behavioral Sciences, University of New Mexico, Albuquerque, NM.

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

CATR: Can you define the term "psychedelics"? How do they work in the brain?

Dr. Bhatt: It's not exact, but you can get a sense of the word's meaning through its etymology, the word "psyche." The idea is that psychedelics allow access to the hidden psyche, hidden realms of the mind. But we can also break the category down in a more scientific way. "Classic psychedelics" are those whose effects largely come from serotonin agonism. These are compounds like psilocybin, LSD, mescaline, and DMT. Then there are compounds whose effects may overlap with classic psychedelics but differ from the classic group in their mechanism of action. These include ketamine and MDMA. With classic psychedelics, we see immediate effects on mood and changes in perception without the cognitive changes or stupor that you might see with opioids or the hyperactivity and huge autonomic surge that you get with cocaine or methamphetamine.

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Expert Interview – Psychedelics and Addiction

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CATR: What are some of the applications of psychedelics being researched now?

Dr. Bhatt: Perhaps the best-known research is on ketamine and esketamine for treatment-refractory depression and acute suicidality. Those results are well publicized. MDMA has some promising early data for treatment of PTSD when combined with psychotherapy. It has many effects in the brain, but one of them is regulation of the amygdala, which is an area of the brain that generates fear responses. The idea is that MDMA allows people to feel safe enough to engage with memories without being overwhelmed by fear. They can process memories rather than running away from them. Psilocybin already has some promising results for distress at the end of life and is now being looked at as an addiction treatment as well (Griffiths RR et al, *J Psychopharmacol* 2016;30(12):1181–1197).

CATR: You were involved in an investigation of psilocybin for the treatment of alcohol use disorder (AUD) that had impressive results. What's the rationale there?

Dr. Bhatt: You are referring to the recent study with Dr. Michael Bogenschutz (Bogenschutz MP et al, *JAMA Psychiatry* 2022;79(10):953–962; see *CATR* Oct/Nov/Dec 2023 for more on this study). It's not intuitive to use a psychedelic as a treatment for addiction, but there are two main reasons why we pursued this avenue. First, there are anthropologic data. Indigenous populations that use psychedelic compounds tend to have low rates of AUDs (Barbosa PCR et al, *Front Psychiatry* 2018;9:136). These are associational data, and it's a big leap to go from sacramental use to medical use, but the results are still intriguing.

CATR: And what was the second reason?

Dr. Bhatt: We have a treasure trove of data on psychedelics going back to the 1950s and 1960s that has been almost entirely forgotten. As early as 1953, Osmond and Hoffer began to use LSD clinically to treat individuals with AUD. They describe participants emerging from their study with new motivation, new ideas, and new goals that ultimately helped them change their relationship to drinking. Other scientists continued the work in a research context until the Controlled Substances Act shut down research in 1970. In fact, a meta-analysis of six LSD studies from the 1960s found that LSD did help people cut down on drinking with a number needed to treat that is better than the medications we currently use, with benefits lasting three to six months (Krebs TS and Johansen PØ, *J Psychopharmacol* 2012;26(7):994–1002).

CATR: But aren't psychedelics addictive themselves?

Dr. Bhatt: At a basic level, classic serotonergic psychedelics are not particularly reinforcing. That's true in animal models and human subjects (Johnson MW et al, *Neuropharmacology* 2018;142:143–166). But that is not to say that these substances can't be misused, because they certainly can be. Mitigating risk of misuse is fairly straightforward within the confines of a research trial where we control medication access and dosage. But I think another important component was our extensive psychotherapy in the trial design.

CATR: Why do you think therapy mitigates the risk of misuse in this context?

Dr. Bhatt: Our study included 12 weeks of psychotherapy, with psilocybin being administered at weeks 4 and 8. Therapy sessions before administration focused on preparation. Our central questions were: "Why are you doing this? What are your goals? What do you hope to gain?" Sessions after drug administration focused on processing and integrating experiences they had: "What sort of meaning did you derive? How can you carry this forward in a positive way?" We never framed the drug as fun or recreational, and I think that really shaped the experiences and perceptions the participants had.

CATR: What kind of experiences did the participants have?

Dr. Bhatt: The experiences varied and were not always fun. They connected with past traumas and a lot of loss, often related to their drinking. This was a placebo-controlled trial, but at the end of the double-blind follow-up period, we broke the blind and participants were offered an additional open-label session. Most people who received the psilocybin were like "Nope. I'm done. I got out of it what I needed—no more for me, thanks." These were not people who were going to go out and start using a bunch of psychedelics because the subjective experience of the trip was negative, even if they ultimately experienced benefits. Even so, the misuse potential is important to keep in mind as states pass legislation allowing psychedelic treatment, like in Oregon (www.tinyurl.com/mpvnjyw9). We need a mechanism of identifying people at high risk of

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misusing psychedelics and to put safety parameters in place. We don't know exactly how to do that yet—there is still research that needs to be done in this area.

CATR: I think the proliferation of ketamine clinics can serve as a precautionary tale.

Dr. Bhatt: In my opinion, for ketamine, clinical implementation got way ahead of the science. Sure, there are good data for treatment of depression and acute suicidality. There are even some data for substance use disorders combining IV ketamine with psychotherapy (Dakwar E et al, *Am J Psychiatry* 2020;177(2):125–133). But we don't know optimal dosing strategies, long-term safety, or how to select the most appropriate patients. *(Editor's note: For more on ketamine, see our Q&A with Dr. Trujillo in this issue.)* There's a similar risk for psychedelics like psilocybin and MDMA, with some differences. Ketamine is FDA approved; it's easy to prescribe and administer. As of now, that isn't an issue with psychedelics; doctors can't just write a script.

CATR: Another concern about psychedelics is whether the benefits are generalizable to diverse populations.

Dr. Bhatt: This is a valid criticism and one of great interest to me. Across all psychedelic trials, 80% of participants are White, and in our study, the median annual income of the participants was about $100,000 (Michaels T et al, *BMC Psychiatry* 2018;18(1):1–14). Clearly, we need to diversify our participant pool. I think certain diversity requirements should be included in research grants. But we also need to do targeted community outreach. For example, the state of New Mexico, where I work, has 23 Indigenous tribes. There is a long history of exploitation and distrust; we need to partner with these groups. Also, as it stands now, treatments are expensive and labor-intensive. I'm not interested in developing a treatment exclusively for the rich and famous. How do we ensure that it is available for anyone who needs it? Part of that is going to be through state funding and grants. It's often the stuff that goes around the drug that makes the treatment expensive. We are looking into measures that might cut costs without sacrificing safety or rigor, such as group-based models and having a single therapist present instead of two.

"Don't be afraid to ask 'What have you heard about psychedelics? What are your thoughts about them?' Most patients will have heard of them; some will be curious to learn more. Occasionally, you might get an angry 'Why are you asking me about that?' A good response is 'I ask all my patients.'"

Snehal Bhatt, MD

CATR: How far away are we from writing a psychedelic prescription? What would need to happen to make this a reality?

Dr. Bhatt: We are still quite a ways away. First, we need to replicate findings in large rigorous studies. If those demonstrate good efficacy and safety, there is the FDA approval process to navigate. In the case of psychedelics, that would require controlled substance rescheduling and likely the development of a risk evaluation and mitigation strategy program. There are also practical considerations. Will psychotherapy be a mandated component? If so, what will the training entail? Who will manufacture the medication? How will it be supplied, distributed, and stored?

CATR: Even though it'll be a while before we're prescribing psychedelics in everyday practice, we are seeing a tremendous interest from patients, largely driven by sensationalized news coverage. How should we discuss psychedelics with patients?

Dr. Bhatt: I agree that the media can blow up these studies and sensationalize them. It's unfortunate, but that's not going to change. So, the responsibility of patient education is going to fall on individual providers. I think it's informative to look back to when cannabis was first starting to be legalized for medical use several years ago; states were opening dispensaries, medical evidence for cannabis efficacy was mostly lacking, media coverage was everywhere, and physicians were caught in the middle. We did an investigation into communication patterns around medical cannabis where we found that very little information was coming from physicians, who felt unprepared to discuss the topic in an informed way. So where did patients end up getting information? Budtenders and insurance companies, and a lot of that information was not evidence based. So, there was a real communication vacuum there, and I think, a lost opportunity.

CATR: And what about microdosing?

Dr. Bhatt: I get asked this question a lot! Microdosing has entered the collective cultural consciousness through the media and, more recently, personal testimonials that are disseminated largely online. We don't have even rough estimates of prevalence, but clearly a lot of people are experimenting with it. Many of them report benefits, but there isn't any research in this area and it's important that our patients know that. I try to strike a balance between validating their experiences and pointing out that we simply don't yet have scientific data when it comes to benefits and, importantly, risks.

CATR: So taking this all together, what can we as providers do?

Dr. Bhatt: We need to engage our patients around psychedelics proactively. Don't be afraid to ask "What have you heard about psychedelics? What are your thoughts about them?" Most patients will have heard of them; some will be curious to learn more. Occasionally, you might get an angry "Why are you asking me about that?" A good standard response is "I ask all my patients. It's all over the news, so I want to make sure you have accurate and up-to-date information." And here is where we can step up, fill in knowledge gaps with evidence-based information. We should be stressing the integral role of intensive psychotherapy in these trials. Unfortunately, patients may read a news story and walk away with the message that they can cure their depression or AUD by taking some psilocybin mushrooms or some other psychedelic drug at home by themselves, or with their friends. But we don't know what sorts of effects that kind of use has. We need to give that message to our patients.

CATR: Any other tips?

Dr. Bhatt: Get comfortable saying "I don't know." The research is in its nascent stages, but for better or worse, patients are hearing all about it. We must impress upon them that many of our questions remain unanswered. Some professional

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organizations are publishing data in this area; one source I particularly recommend is the American Society of Addiction Medicine's weekly newsletter (www.tinyurl.com/3xwzrhwn). Finally, if your patient is requesting information about psychedelic treatment, gather a careful history of recreational psychedelic use. Patients with a history of psychedelic misuse might be particularly interested in psychedelic-assisted treatment but probably warrant additional caution. And you may uncover a condition that could benefit from a nonpsychedelic treatment.

CATR: Are there centralized resources for providers to learn more?

Dr. Bhatt: There is talk of a professional organization forming, but that has yet to happen. If one does, I expect it will be a great repository of information. In the meantime, websites for NYU's Center for Psychedelic Medicine (www.tinyurl.com/54r5udea) or the Johns Hopkins Center for Psychedelic and Consciousness Research (www.hopkinspsychedelic.org) are good resources for upcoming clinical trials that may be an option for patients.

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

Treating Opioid Use Disorder During Pregnancy

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Why treat?

Untreated OUD in the perinatal period is associated with maternal cardiac arrest, intrauterine growth restriction, placental abruption, premature birth, and low birth weight (Nørgaard M et al, *Subst Abuse* 2015;9(Suppl 2):5–11). Additionally, opioid overdoses have emerged as a primary driver of postpartum maternal mortality (Bruzelius E et al, *JAMA* 2022;328(21):2159–2161). Opioid withdrawal can be especially dangerous during pregnancy. The catecholamine surge precipitated by withdrawal induces uterine contractions, diminishing placental blood flow and oxygen supply, which can lead to fetal hypoxia, preterm labor, and even fetal demise (Miller CB and Wright T, *Acad Forensic Pathol* 2018;8(4):865–873).

Effective treatment of OUD during pregnancy, particularly with buprenorphine and methadone, can significantly mitigate these adverse outcomes. Minimizing exposure to illicit opioids not only reduces the risk of overdose, but also is associated with healthier infant birth weight, lower likelihood of premature birth, and decreased intensity of neonatal opioid withdrawal syndrome (NOWS). Moreover, the improved psychosocial stability that comes with treatment decreases the risk of communicable diseases and comorbid substance use, improves maternal nutrition, and encourages engagement in perinatal care (Jones HE et al, *J Subst Abuse Treat* 2008;35(3):245–259).

Patients may ask about medically assisted withdrawal, commonly called medication-assisted "detox," which involves a short taper of buprenorphine or methadone with the goal of ultimately stopping all medication and opioid use. The use of medication is intended to result in fewer opioid withdrawal symptoms compared to stopping opioid agonists cold turkey. While the approach is probably safe for the fetus, it rarely results in sustained abstinence and is associated with high rates of return to illicit opioid use (Terplan M et al, *Obstet Gynecol* 2018;131(5):803–814).

Choosing the right MOUD

Buprenorphine and methadone are both safe and effective in pregnancy. An advantage of buprenorphine is that it results in less severe NOWS. In a landmark study, infants exposed to buprenorphine required 89% less morphine, had a 58% reduction in treatment duration, and had a 43% reduction in length of hospital stay compared to infants exposed to methadone (Jones HE et al, *N Engl J Med* 2010;363(24):2320–2331). Infants exposed to methadone also have been found to have modestly increased rates of preterm birth, small size for gestational age, and low birth weight relative to those exposed to buprenorphine (Suarez EA et al, *N Engl J Med* 2022;387(22):2033–2044).

On the other hand, methadone may be better at retaining patients in treatment over the course of pregnancy. In the study referenced above, pregnant patients on buprenorphine were nearly twice as likely to discontinue MOUD compared to those taking methadone: 33% vs 18% (Jones et al, 2010). Like much of medicine, methadone and buprenorphine have pros and cons. Therefore, medication choice should come from shared decision making, taking patient preference, prior response, and treatment availability into account (Guille C et al, *Psychiatr Res Clin Pract* 2019;1(1):27–31).

Special considerations during pregnancy

Physiologic shifts

Many physiologic shifts occur during pregnancy that affect the pharmacokinetics of buprenorphine and methadone, including:

- Increases in volume expansion and cardiac output
- Decreases in protein binding and drug absorption

These changes tend to peak during the second trimester and persist until delivery (Kazma JM et al, *J Pharmacokinet Pharmacodyn* 2020;47(4):271–285).

Drug metabolism

Drug metabolism increases significantly during pregnancy as well. Surges in progesterone and estrogen trigger the induction of cytochrome P450, leading to reduced half-life and lower peak plasma concentrations of methadone and buprenorphine (McCarthy JJ et al, *J Addict Med* 2018;12(3):241–246). Genetic variations in CYP450 polymorphisms lead to ultrarapid methadone metabolism in up to 44% of pregnant patients, reducing the drug's half-life even further—from up to 59 hours in non-pregnant patients to eight hours in pregnant patients and a mere four to six hours in ultrarapid metabolizers (Badhan RKS and Gittins R, *J Subst Abuse Treat* 2021;130:108521).

Buprenorphine has three active metabolites, unlike methadone, which only has a single inactive metabolite (Brown SM et al, *Anesthesiology* 2011;115(6):1251–1260). These active metabolites might serve as a protective buffer against the increased metabolism, leading to buprenorphine typically needing less active adjustment during pregnancy than methadone.

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Prescribing MOUD

Protocols for starting MOUD in pregnancy are similar to those in the general population, but with the special consideration of minimizing maternal withdrawal given the potential for adverse fetal effects. Whichever medication you and your patient choose, it should be started as soon as possible and continued after delivery.

Buprenorphine

Pregnant individuals under 24 weeks of gestation can usually undergo outpatient buprenorphine induction. Refer your patient to the emergency department if they experience precipitated withdrawal or if their Clinical Opiate Withdrawal Scale (COWS) score goes over 14. Hospitalization is recommended for buprenorphine induction for all patients after 24 weeks of gestation, which is the gestational age at which fetal monitoring can be done efficiently.

The induction procedure is essentially the same as in non-pregnant patients (see *CATR* Nov/Dec 2021):

- Give an initial dose of 2–4 mg once COWS >8
- An additional 2–4 mg can be given every two to four hours for a total of 8–12 mg in the first 24 hours
- The dose can be increased by 8 mg each day, up to a total of 24 mg daily

Buprenorphine doses usually do not need to be increased as much as methadone during pregnancy, though some patients may benefit from slightly higher or more frequent doses; adjust according to your patient's symptoms (Young JL and Martin PR, *Psychiatr Clin North Am* 2012;35(2):441–460).

Recent evidence has found no adverse effects in pregnancy with buprenorphine/naloxone (Link HM et al, *Am J Obstet Gynecol MFM* 2020;2(3):100179). The monoproduct and combination product are both regularly used, so choose whichever is accessible and preferred by your patient.

Methadone

Methadone treatment can be initiated as an outpatient early in pregnancy, typically in the first or early second trimester. Later in pregnancy, methadone is usually started in an inpatient setting, which allows the patient to be in a controlled environment as the medication is titrated and facilitates fetal monitoring.

If the patient presents without symptoms of withdrawal:

- Give a small initial dose of 5–10 mg
- Follow with an additional dose if withdrawal develops

If the patient presents in moderate or severe withdrawal:

- Give an initial 20–30 mg dose
- Provide an additional 5–10 mg every three to six hours, until withdrawal symptoms are relieved or a maximum of 50 mg is reached

Additional symptomatic treatment can be given for any residual symptoms that are present after the maximum methadone dose is reached. Other than avoiding nonsteroidal anti-inflammatory drugs, medication choice and dosing are similar to treating non-pregnant patients. For a quick review of symptomatic treatments, see the "Adjunct Medications for Pregnant Patients" table.

As long as the patient remains in the hospital, on day 2:

- Give the total dose for the previous 24 hours as a single morning dose
- Give a supplement of 5–10 mg later in the day if withdrawal or cravings develop

Repeat this pattern, with small daily increases until the patient is no longer experiencing withdrawal or cravings. Once this maintenance dose is reached, the patient can continue methadone as an outpatient.

Once discharged, adjust doses more slowly—typically 5–10 mg per week. Daily doses commonly exceed 120 mg; in fact, higher doses are associated with better outcomes (McCarthy JJ et al, *Am J Obstet Gynecol* 2005;193(3):606). When possible, methadone should be given twice daily, which leads to steadier plasma concentrations.

Adjunct Medications for Pregnant Patients

Drug	Dose	Targeted Opioid Withdrawal Symptoms
Acetaminophen	650 mg PO Q6H PRN	Pain
Clonidine	0.1 mg PO Q8H PRN	Hypertension and tachycardia
Dicyclomine	20 mg PO Q8H PRN	Abdominal cramps
Hydroxyzine	50 mg PO Q8H PRN	Anxiety or insomnia
Loperamide	4 mg PO x1, then 2 mg PRN after each loose bowel—max 16 mg/24 hours	Diarrhea
Ondansetron	4 mg PO Q8H PRN	Nausea
Pantoprazole	40 mg PO daily	Gastric reflux

Postpartum

Patients should remain on MOUD following delivery; overdose risk peaks six months postpartum and is nearly 10-fold higher for those not on MOUD (Schiff DM et al, *Obstet Gynecol* 2018;132(2):466–474). As the body transitions back to its pre-pregnancy physiology, some patients, particularly those on methadone, may need their dose decreased. However, the total reduction required might be minimal, and some patients may find no need for dose adjustment at all (Pace CA et al, *J Subst Abuse Treat* 2014;47(3):229–232). Follow your patient closely and adjust the dose based on your clinical assessment.

Both buprenorphine and methadone pass into breast milk and have a beneficial effect on NOWS. MOUD have been shown to decrease incidence of NOWS, shorten hospitalization, and improve mother-infant bonding (Bagley SM et al, *Addict Sci Clin Pract* 2014;9(1):19). Given these advantages, encourage breastfeeding for patients on MOUD who abstain from illicit substances and are not HIV positive (Reece-Stremtan S, *Breastfeed Med* 2015;10(3):135–141).

CARLAT VERDICT

The past decade has seen a dramatic increase in the prevalence of OUD in pregnancy and a concomitant rise in adverse events. Buprenorphine and methadone are safe and effective during pregnancy, and their use is associated with a host of benefits. Medication choice and proper dosing involve understanding the physiological changes of pregnancy and an exploration of individual patient needs.

Q&A With the Expert

Ketamine: Use and Misuse

Keith A. Trujillo, PhD

Emeritus Professor of Psychology, California State University, San Marcos, CA.

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

CATR: Dr. Trujillo, you have done research and have published widely on the pharmacology of ketamine. Before we discuss the addiction risks, can you run us through some of the evidence for ketamine's therapeutic effects?

Dr. Trujillo: It's helpful to start with its origins. Ketamine was FDA approved for use in anesthesia in 1970, so we have 50 years of experience with it in medicine. Work on depression began more than 30 years ago in animal models (Trullas R and Skolnick P, *Eur J Pharmacol* 1990;185(1):1–10; Pilc A et al, *Biol Psychiatry* 2013;73(12):1125–1132). Jumping forward 10 years, the first human data on ketamine for depression appeared in 2000 with a small double-blind study showing significant improvement in depression just four hours after an IV ketamine infusion with effects lasting 72 hours (Berman RM et al, *Biol Psychiatry* 2000;47(4):351–354). Subsequent studies have showed significant therapeutic effects at 24 hours that last as long as 7–14 days (Walsh Z et al, *BJPsych Open* 2021;8(1):e19). Ketamine is clearly different than traditional antidepressants. It works in hours instead of weeks with benefits lasting long enough for intermittent dosing. Perhaps most importantly, it can help patients for whom other antidepressants have been ineffective, such as patients with treatment-resistant depression (TRD).

CATR: What was the rationale for looking at ketamine as an antidepressant?

Dr. Trujillo: There was a gradual accumulation of findings pointing to the central role of glutamate in depression. The thought was that ketamine, as a glutamate receptor antagonist, might be able to modulate depression in a novel way. But ketamine acts on a variety of receptor targets and has multiple bioactive metabolites, so we still have questions on whether its antidepressant effects are purely due to glutamate antagonism or something else. And it seems glutamate plays a central role in other psychiatric disorders as well. There is work on potential ketamine treatment for bipolar disorder, OCD, PTSD, anxiety, anorexia, and—perhaps paradoxically—substance use disorders (SUDs).

CATR: That does seem paradoxical. Ketamine itself can be addictive, and misuse can have serious medical consequences.

Dr. Trujillo: That's true. In the United States, we see relatively low ketamine misuse, about 1% of the US population (Van Amsterdam J and Van Den Brink W, *Expert Opin Drug Saf* 2022;21(1):83–94). I think that has to do with its subjective effects. Ketamine tends to produce a mix of rewarding and aversive effects that, for most people, balance each other out and limit high dose or frequent use. This is very different than other illicit drugs like opioids and stimulants, which are powerfully reinforcing. When we're looking at long-term adverse effects, the keys are dose and interval. The higher the dose and the more frequently the drug is taken, the higher the risk. Relative to anesthetic and recreational doses, antidepressant doses are quite low. And the interval is intermittent, so when used properly, we expect low rates of addiction and long-term adverse effects.

CATR: What is "proper" dosing for ketamine in depression?

Dr. Trujillo: Recommended IV ketamine dosing is 0.5 mg/kg given over 40 minutes or so (McIntyre RS et al, *Am J Psychiatry* 2021;178(5):383–399). It should be given in a closely monitored medical setting. There is a lot yet to be determined, but treatment frequency is typically one to three times a week to determine if a patient will respond. Response after four to six infusions is considered successful treatment. Frequency is then usually decreased for maintenance therapy.

CATR: And rates of adverse effects are low when it's dosed this way?

Dr. Trujillo: Yes, we see higher rates of complications with heavy use. A recent analysis found that those who use recreationally had more than 90 times the cumulative exposure to ketamine than those treated for depression; for some, the exposure was as much as a thousand-fold more (Van Amsterdam and Van Den Brink, 2022). Some people use ketamine very occasionally, in party settings at doses that provide mild effects. The risk there is probably low. But others use in binges—they'll buy ketamine, perhaps to use at a party, but then they can't stop until their supply runs out. Ketamine has a short duration of action, so it encourages repeat use. People who use it in this manner are at a substantially elevated risk. The other group at high risk consists of individuals referred to as "psychonauts"—people seeking the deep dissociative effects, known as a "k-hole," that are seen with very high doses. People report near-death experiences, rebirth experiences, losing themselves to become one with the universe, having conversations with God. Some seek that sort of effect, but most are afraid of it; the loss of ego can be very frightening.

CATR: What are the risks of developing ketamine use disorder?

Dr. Trujillo: Ketamine is a DEA Schedule III substance, which is defined as having "moderate to low potential for physical and psychological dependence." Schedule III drugs show less risk than Schedule I or II but do have risk for SUD. And taking large amounts of ketamine, outside of professional supervision, is a risk factor. Indeed, there are several case reports in the medical literature of ketamine use disorder in individuals who used ketamine recreationally, and there is at least one case report of an individual self-medicating with ketamine for bipolar disorder and developing ketamine use disorder after taking large quantities of the drug daily for five years (Liu JX et al, *Am J Addict* 2015;24(1):7–9).

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CATR: What about physical adverse effects?

Dr. Trujillo: The side effects from frequent use are primarily in two domains. The first is cognitive deficits that manifest as impairments in learning, memory, and attention. In people engaged in recreational ketamine use, imaging studies have noted decreased brain volume affecting both gray matter and white matter (Van Amsterdam and Van Den Brink, 2022). The other area is lower urinary tract symptoms (LUTS). These begin with pain during urination, urgency, and occasional incontinence. Continued ketamine use can develop into permanent incontinence and ulcerative cystitis that manifests as persistent pelvic pain and bleeding. Finally, those who use ketamine frequently can also experience abdominal pain, sometimes called "k-cramps."

CATR: Are these effects reversible?

Dr. Trujillo: The full answer is that we don't know, but for most people who use ketamine, the LUTS and the cognitive deficits seem to largely resolve after ketamine is stopped.

CATR: And how does esketamine play into all this?

Dr. Trujillo: Ketamine is a racemic mixture that includes both S-ketamine and R-ketamine in roughly equal amounts. Esketamine is the purified S-enantiomer of ketamine. So, anyone getting racemic ketamine is also getting esketamine, in a way. But esketamine on its own was approved for use in 2018 under the brand name Spravato on a fast-track designation for TRD. In 2020, it was approved for major depression with suicidal ideation or behavior (Miscel NA and Balon R, *J Clin Psychopharmacol* 2021;41(3):233–235). It's normally used intranasally, at 56 or 84 mg. There's a widely used protocol that starts with the induction phase, with twice-weekly administration for four weeks. This is followed by the maintenance phase, which involves weekly administration for four weeks transitioning to either weekly or once every two weeks, depending on the needs of the patient.

"A history of addiction should not be a contraindication for ketamine treatment. Depression is a potentially fatal disorder. Not only might depression go untreated, but someone could turn to the streets to buy ketamine, which could be adulterated with a potentially lethal drug like fentanyl."

Keith A. Trujillo, PhD

CATR: How do ketamine and esketamine compare in terms of addictive and misuse potential? How do the potential long-term adverse sequelae compare?

Dr. Trujillo: Subjective effects at therapeutic doses are similar between ketamine and esketamine—dissociation, dizziness, some sedation. A critical difference in terms of addictive potential comes down to the fact that esketamine can only be given in a clinical setting certified with a risk evaluation and mitigation strategy (REMS) program. The potential for misuse is part of the reason the FDA put a REMS program in place. Between the REMS program and the fact that esketamine isn't available on the illicit market, we don't see esketamine misuse or addiction. And since esketamine isn't being used at very high supratherapeutic doses, the risk of long-term LUTS and neurocognitive deficits are low.

CATR: What are your thoughts on the proliferation of private-pay ketamine clinics, many of which are veering outside of typical treatment standards?

Dr. Trujillo: A quick internet search shows how many of these clinics are out there. Some appear to be legitimate—they have a well-trained psychiatrist on staff, and they offer a broad range of options to patients with TRD. Others appear less legitimate, with websites that tend to be full of flowery language and have a New Age kind of feel. They often speak about personal growth or discovery but not the treatment of a psychiatric disorder.

CATR: Do you have recommendations for patients about how to choose between ketamine clinics?

Dr. Trujillo: When it comes to a serious psychiatric condition like TRD, patients should stick to the experts whenever possible. Academically affiliated clinics are a good place to start. Beyond that, I'd steer clear of places run by doctors without any mental health experience. Clinics should be focused on treating depression, and patients should be presented with a range of options rather than only ketamine. Places that offer oral ketamine should be avoided as well. Some clinics will prescribe oral formulations that come in a lozenge form called a troche (pronounced TRO-key). There's no documented evidence for this form's effectiveness in treating depression, and we can't assume that it is equivalent to the IV form. The bioavailability of oral ketamine is low, around 15%, and first-pass metabolism makes it likely that metabolites are going to be very different between oral and IV delivery. Prescribers offering ketamine troches should get a red flag as going way outside the evidence base. In fact, the FDA recently released an alert concerning the risks of off-label compounded ketamine in which they specifically emphasized the potential dangers of oral formulations (www.tinyurl.com/3a9f59d7).

CATR: What about teleprescribing of ketamine? There have been some horror stories in the lay press (www.tinyurl.com/2ms38f2p).

Dr. Trujillo: Teleprescribing of ketamine took off during COVID, which was a once-in-a-lifetime situation that opened all sorts of avenues that were previously unavailable. Given the nature of ketamine and its mixture of pleasurable and aversive subjective effects that we discussed earlier, I doubt that ketamine is going to lead to an epidemic of addiction like methamphetamine or heroin. On the other hand, our evidence base for ketamine is with IV infusions (or intranasal, in the case of Spravato)

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Three Buprenorphine Dosing Strategies When Transitioning From Other Opioids

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

Buprenorphine is a first-line treatment for opioid use disorder. However, as a high-affinity mu-opioid partial agonist, providers must time its initial administration correctly. If given too early, while other opioids are still in the system, it can precipitate withdrawal symptoms (see *CATR* Nov/Dec 2021).

The standard method of buprenorphine induction involves having patients abstain from opioids and start buprenorphine once they are in mild to moderate withdrawal. Though this method is still the gold standard, the timing can be unpredictable given the possible involvement of fentanyl, fentanyl derivates, and other high-potency opioids. To address this, researchers and clinics have developed two new strategies, microinduction and macroinduction. Below, we will explain the basics of the three methods, detail their advantages and disadvantages, and suggest when to use each one. See the "Buprenorphine Induction Strategies" table for a quick overview of dosing specifics.

Standard induction

This is the most common and best-established induction strategy. The approach here is to treat withdrawal symptoms in the first 24 hours and escalate the dose over the next 24–48 hours while targeting cravings. We recommend this approach for most patients since it is relatively fast and the best studied (Substance Abuse and Mental Health Services Administration, *Treatment Improvement Protocol 63*, revised 2021).

Protocol basics

Quantify the severity of opioid withdrawal using the Clinical Opiate Withdrawal Scale (COWS) (www.tinyurl.com/9nmua377). Have the patient stop opioid use and start buprenorphine once they are experiencing moderate withdrawal symptoms as indicated by a COWS score of ≥8–10:

- Day 1: Give 2–4 mg; repeat every hour or so up to 8 mg or until withdrawal subsides
- Day 2: Give the total taken on day 1 first thing in the morning; give additional 4–8 mg doses up to a total of 16 mg or until cravings subside
- Day 3: Give the total taken on day 2 first thing in the morning; give additional 4–8 mg doses up to a total of 24 mg until cravings subside

Today's street drugs are unpredictable, and street fentanyl can consist of not just fentanyl but also fentanyl derivatives with variable potency and half-lives (see *CATR* Nov/Dec 2021). You may, therefore, need to adjust your induction approach; for example, you may need to give some patients up to 12 mg of buprenorphine on day 1 to treat withdrawal symptoms.

Benefits: Standard induction is the best-established strategy with the most evidence for getting your patient onto buprenorphine. It is also quite fast, allowing your patient to get up to a full treatment dose of 16–24 mg daily in just a few days. Studies have also shown that standard induction can be completed effectively at home (Lee JD et al, *J Gen Intern Med* 2009;24(2):226–232). For tips on home induction, see our Q&A with Dr. Capurso in *CATR* Nov/Dec 2021.

Drawbacks: The biggest drawbacks are the risk of precipitated withdrawal if buprenorphine is given too early and the fact that patients will need to experience some withdrawal symptoms before starting the medication. Also, while quick, standard induction still requires a few days to reach an optimal dose.

When to use: Most patients will do well with standard induction, whether they're in the clinic, in the emergency department (ED), or at home. They need to be able to tolerate moderate withdrawal symptoms; consider microinduction if they can't.

Microinduction

Sometimes called "microdosing" (not to be confused with taking small quantities of psychedelics), "low-dose initiation," or "overlapping," microinduction was developed to minimize the risk of precipitated withdrawal. It works by introducing buprenorphine while the patient is still

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Buprenorphine Induction Strategies

Induction Type	When to Use	Pros	Cons	Suggested Dosing
Standard induction	Most of the time	• Best established/ most evidence • Full treatment dose in two to three days	• Risk of precipitated withdrawal • Quick, but requires two to three days for optimal dose	• Day 1: Initial dose of 2–4 mg when COWS ≥8–10, additional doses up to 8–12 mg • Day 2: Give up to 16 mg • Day 3: Give up to 24 mg
Microinduction	• When transitioning from prescribed opioids • With patients unable to tolerate withdrawal symptoms in outpatient setting	Minimal precipitated withdrawal	Requires seven or more days until full dose	Example protocol: • Day 1: 0.5 mg daily • Day 2: 0.5 mg BID • Day 3: 1 mg BID • Day 4: 2 mg BID • Day 5: 2 mg TID • Day 6: 2 mg QID • Day 7: 4 mg TID and stop opioid agonists • Day 7+: Titrate to dose needed to eliminate cravings
Macroinduction	Emergency department (ED) patients at high risk of overdose and with history of poor follow-up	Reaches full dose quickly (first day)	• Least evidence • Should be done in the ED setting • Risk of precipitated withdrawal	• Initial dose of 4–8 mg when COWS ≥8–10 • One additional large dose of 16–24 mg

Three Buprenorphine Dosing Strategies When Transitioning From Other Opioids

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on full-agonist opioids, but at doses small enough not to cause much precipitated withdrawal. The dose is raised in small increments so that the body habituates to the presence of both partial and full agonists. Eventually, once the buprenorphine dose is high enough (usually 8–12 mg), the full agonist can be discontinued.

Protocol basics

Patients remain on full opioid agonists, illicit or prescribed, while buprenorphine is slowly increased over a week or so. There are several protocols to choose from, including sublingual, transdermal, and IV options (Jablonsky LA et al, *Drug Alcohol Depend* 2022;237:109541; Ahmed S et al, *Am J Addict* 2021;30(4):305–315). Protocols can get complicated, especially in a clinic setting, so these patients are seen daily or every other day until opioid agonists are stopped. Here is a sublingual buprenorphine protocol that you might follow:

- Day 1: Give 0.5 mg daily
- Day 2: Give 0.5 mg BID
- Day 3: Give 1 mg BID
- Day 4: Give 2 mg BID
- Day 5: Give 2 mg TID
- Day 6: Give 2 mg QID
- Day 7: Give 4 mg TID; stop opioid agonists

Benefits: The main benefit of this approach is that it minimizes the risk of precipitated withdrawal. This makes for a more comfortable experience for your patient and might lead to improved treatment adherence and therapeutic rapport.

Drawbacks: Reaching a full treatment dose of 16–24 mg takes seven days or more, essentially leaving the patient undertreated during that time. Additionally, cutting sublingual strips into small pieces can be difficult, and transdermal formulations are more expensive.

When to use: Consider this method when transitioning patients from prescribed opioids like methadone or oxycodone. Microinduction can be useful for patients who have difficulty adhering to the standard protocol, either because of difficulty tolerating withdrawal symptoms or a home environment with easy access to opioids.

Macroinduction

A relatively new approach, macroinduction is designed to get patients on a full dose of buprenorphine as quickly as possible. The approach starts the same as standard induction, with buprenorphine introduced once the patient is in moderate withdrawal; however, after the first 4–8 mg dose, a large single dose of 16–24 mg is given.

Protocol basics

Have the patient stop opioid use and start buprenorphine once they are in moderate withdrawal as indicated by a COWS score ≥8–10 (Herring AA et al, *JAMA Netw Open* 2021;4(7):e2117128):

- Give first dose of 4–8 mg, then wait 30–60 minutes
- As long as there is no precipitated withdrawal, give a single large dose of 16–24 mg for a total of 32 mg
- This dose should be large enough to curb cravings and provide overdose protection for two days

Benefits: This approach gets patients on a full treatment dose of buprenorphine very quickly, usually in a single visit of just a few hours. Despite the large dose, rates of precipitated withdrawal are similar to those seen in standard induction (Herring et al, 2021).

Drawbacks: Of the three approaches, macroinduction has the least amount of evidence and has only been studied rigorously in an ED setting with close medical monitoring. Like the standard approach, macroinduction carries a risk of precipitated withdrawal.

When to use: Consider macroinduction for patients in the ED, especially those who have a high risk of opioid overdose or a history of poor follow-up.

CARLAT VERDICT

The standard buprenorphine induction has the most evidence behind it and should be your go-to. Consider microinduction for patients transitioning to buprenorphine from prescription opioids or those who have difficulty adhering to the standard approach. Macroinduction can be used for patients in an ED setting, especially if they have a history of poor treatment adherence.

Expert Interview – Ketamine: Use and Misuse

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performed in professional healthcare settings. We have no frame of reference in terms of safety when patients are taking ketamine at home. Could there be a future in which ketamine is given at home, perhaps through teleprescribing? Maybe, but there would have to be an evidence base to support its efficacy and safety before I would ever recommend it, and we're nowhere close to that in terms of the research.

CATR: Most of our readers won't be prescribing ketamine themselves. How can they help mitigate some of the risks we've discussed here?

Dr. Trujillo: Let's say you're seeing a patient who is thinking about starting ketamine. Or maybe you think ketamine might be a good option for a patient you are seeing with TRD. The first thing to ensure, just like with any medication, is that the patient is fully informed of the risks and benefits before starting. That's just basic prescribing, but with ketamine it's so important because there are so many cultural narratives floating around out there. Ask what your patient has heard. What is their understanding of ketamine? What are their concerns? And it helps to obtain a consultation if you don't have experience as a ketamine prescriber yourself; that way you can inform patients about what to expect. For example, there are basics that all ketamine and esketamine prescribers should adhere to: monitoring of vital signs, observation for at least two hours following a dose, no driving until the next day. Patients need to know about these logistical issues beforehand. And patients should be carefully prescreened. Do they have a history of ketamine misuse? What about misuse of other club drugs or hallucinogens? What about addiction in general?

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Research Updates

OPIOID USE DISORDER

Buprenorphine versus Methadone for Prescription Opioid Use Disorder

Richard Moldawsky, MD. Dr. Moldawsky has no financial relationships with companies related to this material.

REVIEW OF: Jutras-Aswad D et al, *Am J Psychiatry* 2022;179(10):726–739
STUDY TYPE: Open-label, pragmatic, noninferiority, randomized controlled trial

Buprenorphine/naloxone (BUP) and methadone are mainstays of opioid agonist therapy for opioid use disorder (OUD). But most of the data backing this up come from studies of patients who use heroin. It isn't known how generalizable these findings are for patients using other opioids. Moreover, BUP is usually taken at home, whereas methadone tends to be closely supervised. Researchers in this study were interested in how closely supervised methadone treatment compares with flexibly dosed BUP for prescription-type OUD (POUD).

Researchers recruited participants with POUD and randomized them to receive BUP (n=107) or methadone (n=108). BUP was started between 4 mg/1 mg and 12 mg/3 mg per day, and methadone was started at 30 mg per day. The titration schedule of each medication and whether participants could have "take-home privileges" were decided at the discretion of the research staff. The study was a noninferiority trial, meaning that the analysis was designed to determine if BUP is at least as good as methadone for treating POUD. The primary outcome measure was opioid use determined by urine drug screens collected every two weeks for 24 weeks.

The average maximum doses were 20.3 mg for BUP and 81.8 mg for methadone. Of the 107 who started BUP, 71 completed the 24 weeks; of the 108 who started methadone, 79 completed. Some of the participants (22% in the BUP group and 12% in the methadone group) chose to switch the medication they were receiving. 73% of the BUP group were able to take meds home, compared with 32% of the methadone group.

The primary outcome measure showed that, of the completers, 24% of the urine drug screens in the BUP group were drug-free, compared to 18.5% of the screens in the methadone group. Adverse reactions were minimal in both groups; most common (6%) were mild to moderate withdrawal symptoms.

The researchers concluded that flexibly dosed BUP, mostly taken at home, was at least as effective in treating POUD as closely supervised methadone treatment. There were more dropouts and medication switches in the BUP group, though a post-hoc analysis showed that the BUP group had more negative urine drug screens early in the trial, presumably because they were able to reach a therapeutic dose more quickly.

CARLAT TAKE

Flexibly dosed BUP was at least as good as methadone for the treatment of POUD. BUP has the advantage of being easier to take at home and greater overall accessibility, but retention was slightly better with methadone. Given that both treatments emerged as viable, feel free to recommend either one for your patients with POUD.

Opioid Use Disorder Treatment During the Peripartum Period

Gregory Nikogosyan, DO. Dr. Nikogosyan has no financial relationships with companies related to this material.

REVIEW OF: Mason I et al, *J Addict Med* 2022;16(4):420–424
STUDY TYPE: Retrospective cohort study

Optimizing opioid use disorder (OUD) treatment during pregnancy is of the utmost importance; in addition to the usual risks of overdose and death to the pregnant patient, untreated OUD risks preterm labor, intrauterine growth restriction, and fetal death. Co-locating obstetric and OUD care has been shown to improve outcomes, but how long these benefits last and whether they carry over into subsequent pregnancies is unknown (Meter M et al, *J Addict Med* 2012;6(2):124–130).

To find out, researchers performed a retrospective cohort study of 42 patients with a diagnosis of OUD who received care at their multidisciplinary obstetric and addiction clinic for more than one pregnancy. The clinic provided prenatal care, initiation and management of buprenorphine and methadone, and weekly group therapy, as well as access to a team of social workers, psychiatrists, counselors, and nurses. The primary outcome was rate of medication for OUD (MOUD) at the first pregnancy compared to subsequent pregnancies. Secondary outcomes were rate of neonatal opioid withdrawal syndrome (NOWS) and length of hospital stay.

The results clearly showed that remaining in interdisciplinary care was associated with improved OUD outcomes in subsequent pregnancies. Participants were six times more likely to be on MOUD treatment before subsequent pregnancy as compared to their first pregnancy (odds ratio [OR]=6.48 [95% confidence interval (CI), 2.52–16.64]). Unsurprisingly, the improved MOUD adherence also resulted in lower rates of prenatal urine drug screens positive for illicit substances (64% vs 36%, OR 0.33 [95% CI, 0.14–0.78]). Other outcomes, such as rates of NOWS, length of hospital stay, and involvement of child protective services, were not significantly different.

The findings are compelling, though the study's small cohort is a major limitation. And the authors acknowledge that future studies should utilize neonatal outcomes other than NOWS, which is expected from intrauterine exposure to both MOUD and illicit opioids. Finally, receiving obstetric and OUD care from separate providers is the norm; however, authors did not compare their findings with those of patients receiving care separately. We therefore don't know how much benefit patients derived from co-locating these services versus accessing them separately.

CARLAT TAKE

Good peripartum OUD treatment is associated with better outcomes. This study shows, albeit with a small sample size, that good OUD treatment during a first pregnancy can carry into improved outcomes in subsequent pregnancies. Our goal should be to continue to aggressively treat OUD in pregnant patients and do what we can to help them remain in treatment.

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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. What is the recommended maximum daily dose of buprenorphine for pregnant patients (LO #1)?
   [ ] a. 24 mg [ ] b. 12 mg [ ] c. 8 mg [ ] d. 4 mg

2. According to Dr. Bhatt, what is a limitation of clinical trials that have been completed on the use of psychedelics in psychiatric treatment (LO #2)?
   [ ] a. High misuse potential due to the addictive nature of psychedelics
   [ ] b. Ethical concerns because the median annual income of participants in psychedelic trials is under $50,000
   [ ] c. Moving too quickly into clinical implementation without evidence from longitudinal studies
   [ ] d. Unclear effects across different population groups because most participants in psychedelic trials have been White and wealthy

3. Which buprenorphine induction strategy carries the lowest risk of precipitated withdrawal (LO #3)?
   [ ] a. Macroinduction
   [ ] b. Standard induction
   [ ] c. Microinduction
   [ ] d. Either macroinduction or standard induction

4. According to a 2022 study of pregnant patients receiving medications for opioid use disorder (MOUD), what was the most significant benefit of receiving interdisciplinary care (LO #4)?
   [ ] a. Lower rates of neonatal opioid withdrawal syndrome (NOWS)
   [ ] b. Decreased incidence of preterm labor and low birth weight
   [ ] c. Increased use of MOUD before subsequent pregnancies
   [ ] d. Shorter duration of hospital stays

5. True/false: An advantage of buprenorphine over methadone in pregnancy is that it leads to less intense NOWS (LO #1).
   [ ] a. True [ ] b. False

6. According to Dr. Trujillo, what is the recommended IV ketamine dosing for the treatment of depression (LO #2)?
   [ ] a. 0.5 mg/kg
   [ ] b. 1 mg/kg
   [ ] c. 0.25 mg/kg
   [ ] d. 0.1 mg/kg/hr

7. Which of the following statements about buprenorphine induction strategies is true (LO #3)?
   [ ] a. Rates of precipitated withdrawal for macroinduction are comparable to those for standard induction
   [ ] b. Macroinduction minimizes the risk of precipitated withdrawal symptoms
   [ ] c. Standard induction is the best-established strategy but is being cast aside in favor of microinduction and macroinduction, which can be better tailored to patients
   [ ] d. Macroinduction has been shown to be a safe way to start buprenorphine from home

8. What was a notable takeaway of a 2022 study of buprenorphine/naloxone (BUP) and methadone for prescription OUD (LO #4)?
   [ ] a. The methadone group had more medication switches
   [ ] b. The methadone group had more negative urine drug screens early on
   [ ] c. The BUP group had fewer dropouts
   [ ] d. The BUP and methadone groups showed similar treatment success rates

Expert Interview – Ketamine: Use and Misuse

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CATR: Is history of addiction a contraindication for ketamine treatment?

Dr. Trujillo: In my opinion, it shouldn't be. Depression is a potentially fatal disorder. I'd be wary about automatically excluding anybody. I think patients with SUD should be closely monitored, just like any other patient, and the addictive and misuse potential of ketamine should be discussed thoroughly. Withholding treatment from someone who could benefit can have devastating consequences on its own. Not only might depression go untreated, but someone could turn to the streets to buy ketamine. Unfortunately, what they purchase could be adulterated with a potentially lethal drug like fentanyl, or it could be a different drug altogether. And even if one obtains the correct product, there's no guarantee it's the correct dose.

CATR: Any specific suggestions for patients with a history of SUD getting ketamine?

Dr. Trujillo: Opioid contracts are commonly used in pain clinics, and some of those same principles can be applied when starting ketamine. And if treatment needs to be stopped, whether for doctor shopping, buying off the street, or simply inadequate antidepressant effect, make sure patients know about alternative approaches like transcranial magnetic

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Expert Interview — Ketamine: Use and Misuse
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stimulation or ECT. Importantly, have these conversations at the outset. Also, keep in mind that people sometimes use substances because they are depressed. If you can find a good treatment, and that might be ketamine, substance use might decline. And that takes us to the paradox of ketamine as a possible SUD treatment.

CATR: How might ketamine work to treat SUD?

Dr. Trujillo: Research in the area is preliminary but promising. Most studies have been done in patients with opioid or alcohol use disorders, and the intervention was often intensive ketamine-assisted psychotherapy (Ezquerra-Romano I et al, *Neuropharmacology* 2018;142:72–82). It's not unlike the paradigm being investigated for psilocybin-assisted psychotherapy for SUD. (*Editor's note: See our interview with Dr. Bhatt in this issue.*) More work needs to be done to tease out ketamine's effect versus therapy's effect versus any synergistic combination of the two. Ketamine can be an important piece of the treatment puzzle, but just like anything else, it needs to be placed in the context of the whole patient.

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

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