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Editor-in-Chief

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Learning Objectives

After reading these articles, you should be able to:

1. Enhance psychiatric outcomes by strengthening the therapeutic alliance.
2. Demonstrate an understanding of the off-label options for treating common psychiatric conditions.
3. Implement a protocol for pairing ketamine with therapy in treatment-resistant depression.
4. Summarize some of the current research findings on psychiatric treatment.

Off-Label Strategies for Common Psychiatric Conditions

Chris Aiken, MD, Editor-in-Chief of The Carlat Psychiatry Report. Assistant Professor, NYU Langone Department of Psychiatry. Practicing psychiatrist, Winston-Salem, NC.

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

FDA approval is often seen as a “gold standard,” but not all approved medications are first line in their class. In this article, I’ll highlight areas where an off-label option might be preferred over those with FDA approval.

PTSD

Before reviewing medications for PTSD, it’s important to note that psychotherapy is generally considered to be the first-line treatment. When therapy and selective serotonin reuptake inhibitor (SSRI) antidepressants are compared head-to-head, therapy has greater and longer-lasting benefits in PTSD (Storm

Highlights From This Issue

Feature article. Chris Aiken looks at off-label options that outshine their FDA-approved counterparts.

Feature QA. David Mintz shows us how a psychodynamic approach enhances medication outcomes.

QA on page 5. Kyle Greenway describes a protocol for ketamine-assisted psychotherapy.

Research updates starting on page 9. New research on antidepressant efficacy, trichotillomania, and delirium.

MP and Christensen KS, *Dan Med J* 2021;68(9):A09200643).

Two SSRI antidepressants are approved for PTSD (sertraline 50–200 mg/day and paroxetine 20–50 mg/day), but
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Q&A
With
the Expert

How to Incorporate Psychodynamic Principles Into Your Practice

David Mintz, MD

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

TCPR: What qualities in a provider contribute to enhanced patient outcomes?

Dr. Mintz: Warmth, empathy, our investment in the patient, and our optimism about treatment. This latter one is tricky when you work with treatment-resistant patients, where medications are unlikely to do the work alone. But you can have optimism about the patient’s role in the treatment, about what happens when you foster an alliance that mobilizes the patient’s agency.

TCPR: What would you say to a patient with depression as you prescribe an antidepressant?

Dr. Mintz: If it’s their first antidepressant, it makes sense to talk up the medication. There is, after all, some realistic hope that they will recover with it. But where I work at Austen Riggs, most of the patients have already failed
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multiple medications. What I want is for them to feel like they have agency in the recovery process. Otherwise, they are just waiting to be fixed.

TCPR: That's unlikely to happen with meds. I recall one study where the chance of remission after five failed medication trials was zero (Petersen T et al, *J Clin Psychopharmacol* 2005;25(4):336–341).

Dr. Mintz: Yes, these patients are often demoralized about treatment and they don't respond well when we come across with too much optimism (Priebe S et al, *BMC Psychiatry* 2017;17(1):26). I'll say that medications are helpful, but they are not everything. If they really want to get better, they've got to do the rest. That leads us into discussions of antidepressant lifestyle and psychotherapy and other psychosocial factors that promote optimal outcomes.

TCPR: What psychological factors predict a good response on the patient's side?

Dr. Mintz: Readiness to change is a big one. In a large trial of a benzodiazepine in panic, patients who were ready to change and got the placebo had better outcomes than those who got the benzo but entered the study with little readiness to change.

"Readiness" was assessed with answers to prompts like "I have problems and I really think I should work on them." Those with low scores had little motivation to work on the problems and saw them as something outside of their control and responsibility (Beitman BD et al, *Anxiety* 1994;1(2):64–69).

TCPR: How do you talk to patients about their readiness for change?

Dr. Mintz: I explore their ambivalence. Most patients have some ambivalence about treatment and about medications. So, I ask "What does it feel like to take medications?" They may, for example, say "I can't stand it because I hate to be dependent." Then I'll ask "How far back does this go? Do you have any ideas about why it started?" Often that leads to problems with their early caregivers. Patients who are ambivalent about caregiving often had parents with some early adversity in those important relationships. If they share those experiences with me, I tend to bring it back to the present, asking "How does that affect the way you relate to caregivers now?"

TCPR: I'm guessing most patients who come for an evaluation for treatment-resistant depression are not expecting to talk about these things.

Dr. Mintz: That's true, but it's important to start the conversation about psychological factors early on. If you wait to explore this until there is frustration with how the treatment is going, it is much more likely to make the patient defensive. You want to come at the topic from a position of curiosity and set the stage that you are interested in learning about psychological factors that affect their recovery. Often patients deeply appreciate that you are trying to grasp them as a human and not just as a DSM diagnosis.

TCPR: What about external factors that reinforce the illness?

Dr. Mintz: There are all kinds of secondary gains that reinforce illness, from getting out of responsibilities to disability benefits. Often, however, the patient is not directly conscious of the gain, and you have to handle this tenderly. I'll ask "Is there anything you would stand to lose if you got better?" Two thirds don't have an answer, but for others it opens up a conversation. We may not address it right away, but I'll flag it and later will raise it with empathy: "I could see why it would be hard to give that up."

TCPR: Most of us probably think our therapeutic alliance is better than it is. How can we look for signs that something is wrong?

Dr. Mintz: At the first session, I talk to the patient about the importance of the alliance for promoting positive outcomes. I'll say "One of the implications of a strong alliance is that if I am doing something that you don't like, I need you to tell me. How good are you at that?" If they are not good at speaking up for themselves, I'll say "From time to time I'll ask you about how we're doing together because that is going to influence how well the medications are working."

TCPR: What kinds of things do patients complain of?

Dr. Mintz: A common complaint is that they felt like I leapt to a conclusion too quickly or I didn't hear something. Often just talking about it makes things better.

TCPR: It sounds like we need to be receptive to criticism, including from patients who have distorted perceptions.

Dr. Mintz: Yes. We need to acknowledge our contribution to why things are going awry just as we expect the patient to. The first thing to do is to ask ourselves "How is the patient right?" Not "Is the patient right?" There are times

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EDITORIAL INFORMATION

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when we make genuine errors and need to apologize, but more often this isn't a flaw. It's a subtle mismatch. It's about our limitations. When we presume a kind of expertise that we don't have, we undermine the patient's authority and create conditions for distrust.

TCPR: I don't want to trivialize these therapeutic techniques as a placebo, but it sounds like they would enhance the placebo effect in treatment.

Dr. Mintz: Yes, placebo contributes substantially to our outcomes, so we need to understand how to maximize it. In research there is an attempt to minimize the placebo effect, but even there it often outsizes the effects of the treatment.

TCPR: How powerful is the placebo effect?

Dr. Mintz: In depression, the placebo effect accounts for nearly half of an antidepressant's effect. But that may be an underestimate because there is a publication bias where negative studies with large placebo effects tend not to get published. If we look at a less biased sample, like the FDA database of registered trials, the placebo effect accounts for as much as 76%–81% of antidepressant effect. Another way to look at it is through effect size. Antidepressants have a small effect size (0.30–0.35), just barely noticeable to the casual observer, while the placebo effect size is large (1.05), suggesting it contributes three times as much as the actual drug in depression. In other disorders like mania and psychosis it is smaller but still high, with the placebo contributing around twice as much as the active treatment.

TCPR: Isn't the placebo effect baked into every medication we prescribe?

Dr. Mintz: Not automatically. You can give a sugar pill and get no effect at all, or things may get worse. Part of the "placebo" effect is the natural course of illness, and some of it depends on patient factors that are beyond our control. But a lot of the placebo effect varies by provider.

TCPR: How so?

Dr. Mintz: Back in the 1980s, a large trial funded by the National Institute of Mental Health compared antidepressant medication with two kinds of psychotherapy and placebo. The main outcome was that all the active treatments were equivalent and probably the combination of medication and psychotherapy was a little more effective than either alone. But when they looked at the data through the lens of the provider, a new pattern emerged. If a provider got positive results with one patient, they tended to get positive results with all of their patients—regardless of whether medication or placebo was used. And if someone got a poor result, they tended to get poor results across the board. When they stratified the providers by outcome, the doctors who were in the highly effective group got better results with placebo than the doctors in the bottom group got with an active drug.

TCPR: What do we need to do to move into the highly effective group?

Dr. Mintz: We don't know exactly what they were doing, but one branch of this study compared outcomes based on the treating doctor's perspective. Outcomes were better when the doctor had a more psychological understanding of depression as opposed to a more reductionistically biomedical view. This study lumped all the clinicians together—whether they were in the psychotherapy or the medication arm—so we don't know how well that would hold up for psychopharmacology work, but other studies suggest it does.

TCPR: Tell us about that.

Dr. Mintz: One study enrolled college students with depression, who were told that the aim of the study was to determine if their depression was psychological or biological (Kemp JJ et al, *Behav Res Ther* 2014;56:47–52). Somebody in a white coat came in and did a sham cheek swab and came back 15 minutes later. Then the students were randomly informed that their depression was either psychological or biological and genetic in its origins. Contrary to expectations, and to some other studies, telling students that their depression was biological did not reduce their self-blame. But more importantly, the students who received the biological explanation experienced an increase in prognostic pessimism. In other words, they felt more hopeless and helpless, as if they were not going to get better because depression was part of who they were. This is in line with another study, which found that patients with a more biological frame of mind were less likely to recover from depression (Sullivan MD et al, *J Am Board Fam Pr* 2003;16:22–23).

TCPR: What are some psychosocial factors about the medication—or the way the patient takes it—that may enhance the outcome?

Dr. Mintz: One thing I do is to give choices. In one study, patients who were hospitalized for depression were randomized into two groups. One group took escitalopram once a day—the way it is usually delivered. Patients in the other group were given a choice of taking the medication once a day or three times a day. Medically, that is a meaningless choice, but just being given that choice more than doubled the likelihood that the patient would still be taking the antidepressant at three months post-discharge (Woolley SB et al, *J Clin Psychopharm* 2010;30:716–719). This doesn't mean giving the patient all the benzos they think they need. But where we have reasonable options, we should hand the choice over to the patient.

TCPR: On the other hand, can medications be countertherapeutic on a psychological level?

Dr. Mintz: I think this is one of the most underappreciated challenges facing psychiatrists. Imagine a patient who wants more medications. Every time you add one, they say it's helpful, but you find yourself wanting to put on the brakes. Something just feels icky. What happens is that the patient is becoming progressively deskilled because emotionally, they are now increasingly relying on medications rather than more mature coping strategies. And so, to the extent that you keep prescribing without doing anything else, you are participating in that patient becoming a chronic patient.

“When we presume a kind of expertise that we don't have, we undermine the patient's authority and create conditions for distrust.”

David Mintz, MD

TCPR: This doesn't have to do with whether or not their regimen is evidence based. It's about their relationship to it.

Dr. Mintz: Yes. One sign of this is that the symptoms are getting better, but the patient is not getting better. They are not more functional.

TCPR: How do you assess “functioning” with your client?

Dr. Mintz: I don't generally start an interview by asking about symptoms. I'll start with “Where are you trying to get in your life and how do your symptoms get in the way of that?” Then it is easier to see when treatment is addressing symptoms but is not getting them closer to the patient's broader aims in life.

TCPR: Thank you for your time, Dr. Mintz.



Off-Label Strategies for Common Psychiatric Conditions

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when you dig into the evidence, both of these FDA-approved options have strikes against them. Sertraline was effective in only two out of seven controlled trials, enough to get it approved, but not enough to show any benefit in meta-analyses that included the unpublished, negative trials (Hoskins M et al, *Br J Psychiatry* 2015;206(2):93–100). Paroxetine has enough positive trials to pass the efficacy mark, but its tolerability is poorer than other antidepressants in PTSD.

Two off-label options worth considering first line are fluoxetine (20–40 mg/day) and venlafaxine (75–225 mg/day). Both had positive results in meta-analyses and rank first line in many treatment guidelines. When all side effects (including withdrawal problems) are considered, fluoxetine is the best tolerated of the two.

For patients with prominent nightmares or nocturnal awakenings, prazosin is a good option, and some guidelines recommend it first line for these features. Prazosin also improves daytime hyperarousal, and it surpasses the antidepressants in at least one important way. Prazosin worked in both military and civilian populations, while the antidepressants worked mainly in women with civilian trauma (Bajor LA et al, *Psychiatry Res* 2022;317:114840). However, prazosin also has negative trials.

Prazosin has a wide dose range, and that range stretched higher in studies of men (max 25 mg/day) than women (max 12 mg/day). Start at 1 mg QHS and raise by 1–2 mg every four to seven days based on response and tolerability. Around 25% of the dose can be given in the morning after reaching a daily dose of 3–5 mg. Check blood

Metformin and the GLP-1 Agonists for Antipsychotic Weight Gain		
Medication	Dosing	Notes
Liraglutide (Saxenda for weight loss or Victoza for diabetes)	Start 0.6 mg SC injection QD, raise by 0.6 mg every week to target of 3 mg QD (independent of food)	Best-studied GLP-1 in psychiatric populations, goes generic soon
Metformin	Start 500 mg QD with food, raise to 1000 mg/day after a week, max 2000 mg/day	Efficacy is greater when started early in the course of antipsychotic treatment
Semaglutide (Wegovy for weight loss or Ozempic for diabetes)	Start 0.25 mg SC injection Qweek, raise by 0.25–0.5 mg every four weeks to target of 2.4 mg QD (independent of food)	Greater efficacy than liraglutide, but higher risk of intestinal blockage
Tirzepatide (Zepbound for weight loss or Mounjaro for diabetes)	Start 2.5 mg SC injection Qweek, raise by 2.5 mg every four weeks to target of 5, 10, or 15 mg Qweek (independent of food)	Recently approved for weight loss (2023), unstudied in psychiatric populations

pressure and pulse and monitor for falls during titration. If a patient is taking other antihypertensives, consult with the provider managing those and consider tapering them after titrating prazosin.

CARLAT VERDICT

PTSD benefits from a personalized approach. Start with prazosin for prominent nightmares and sleep disruption. For general symptoms, fluoxetine, venlafaxine, and paroxetine are top choices, and fluoxetine has the best tolerability.

Antidepressant Augmentation

The FDA-approved options for antidepressant augmentation are limited to antipsychotics and esketamine. The five approved antipsychotics are aripiprazole 5–15 mg/day, brexpiprazole 2–3 mg/day, cariprazine 1.5–3 mg/day, olanzapine 5–15 mg/day with fluoxetine, and quetiapine 150–300 mg/day. Risperidone (0.5–3 mg/day) also has good evidence but is not clearly better than the approved options. The folate

supplement L-methylfolate (Deplin, 7.5–15 mg/day) is FDA approved as a “medical food” for antidepressant augmentation, which is a less rigorous standard than approval as a medication.

Notably absent from that list is lithium, which is only approved in bipolar disorder despite ranking first line for antidepressant augmentation in five treatment guidelines (Taylor RW et al, *Int J Neuropsychopharmacol* 2020;23(9):587–625). Studies vary on whether lithium or the antipsychotics are more effective, but in the short term it's fair to say that both have comparable benefits and tolerability (Vázquez GH et al, *J Psychopharmacol* 2021;35(8):890–900).

Lithium's main advantage is found in long-term studies, where it reduces the risks of suicide, psychiatric hospitalizations, and depressive recurrence in both unipolar and bipolar disorders (Undurraga J et al, *J Psychopharmacol*

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Q & A
With
the Expert

Ketamine-Assisted Therapy Kyle T. Greenway, MD, MSc

Assistant Professor of Psychiatry at McGill University. Director of the ketamine-assisted therapy program at Jewish General Hospital, Montreal, Canada.

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



Editor's note: Except where noted, we use "ketamine" to refer to both forms of the drug: intravenous ketamine and intranasal esketamine (ie, Spravato, the FDA-approved version of the drug).

TCPR: What type of patient is best suited for the ketamines?

Dr. Greenway: Treatment-resistant depression is where we have the best evidence, which means the patient has not recovered after two antidepressant trials (at least six weeks at a therapeutic dose). That is for unipolar depression. In bipolar depression, the evidence for ketamine is emerging. The other indication is in depression with suicidality (Kritzer MD et al, *Expert Opin Drug Saf* 2022;21(6):725-732). There is some suggestion that ketamine's benefits in suicidality are partially independent of its mood benefits.

TCPR: When should we avoid the ketamines?

Dr. Greenway: Well, treatment-resistant depression is a heterogenous condition, and comorbidities are common here. The one we worry about most is a current substance use disorder (beyond nicotine) or anyone who is at high risk for a substance use disorder. We don't want to set off an iatrogenic use problem (Le TT et al, *J Psychiatr Res* 2022;151:476-496). Another concern is psychosis. I would avoid the ketamines in people with psychotic symptoms until we know more about ketamine's safety there.

TCPR: What about medical risks?

Dr. Greenway: The major issue is increased blood pressure and pulse. So ketamine is not a good idea if someone has had an aneurysm or a recent heart attack or cerebral hemorrhage. But most people can tolerate their blood pressure going up by 20 or 30 points for 40 minutes. If I think the patient could tolerate a 40-minute brisk walk, then it is probably safe.

TCPR: How should we choose between esketamine and ketamine?

Dr. Greenway: Ketamine is the original racemic drug, which is made up of 50% esketamine and 50% arketamine. Ketamine is given off-label as an IV therapy, while esketamine is given intranasally as the branded Spravato. Often the choice comes down to availability. Esketamine is more expensive, but also more likely to be reimbursed by insurers. However, in terms of efficacy and tolerability, all the preliminary evidence we have that indirectly compares these two points slightly in favor of IV ketamine, which is the form I use in Canada (Bahji A et al, *J Affect Disord* 2021;278:542-555).

TCPR: In the US, we'd have to refer to a ketamine clinic. Are there any red flags to look for in terms of quality?

Dr. Greenway: Yes. One of them would be that the clinics are overly biomedical in their orientation or are staffed only by anesthesiologists. They may not have the training to assess and monitor all the comorbidities that go along with treatment-resistant depression. At the other extreme, some clinics may be operating out of a psychedelic paradigm and may be loose with the doses and protocols. For example, they might give IV doses in the clinic and sublingual doses for the patient to take at home, perhaps with a therapist on Zoom in front of them. Clinics need to have protocols in place to avoid diversion.

TCPR: Are there any psychiatric medications that can't be combined with the ketamines?

Dr. Greenway: There are no absolute contraindications, but one class to consider stopping is gamma-aminobutyric acid (GABA) agonists like benzos and Z-drugs. Ketamine is thought to both raise and block glutamate transmission, and GABA and glutamate interact in complex ways. In theory, GABA agonists may blunt this mechanism, and there is evidence that benzodiazepines reduce the acute psychological effects of ketamine, particularly in high doses (Andrashko V et al, *Front Psychiatry* 2020;11:844). Benzos have good evidence in acute depression, but their long-term use is controversial and may even worsen the illness. So that's another reason to consider stopping a benzo before ketamine. It's also a good opportunity to come off other kinds of irrational polypharmacy that aren't clearly helping the patient.

TCPR: And how do you taper the benzo?

Dr. Greenway: The conventional wisdom is to treat the depression first before attempting a taper, but we've found that the ketamine process itself is an excellent occasion to try to get people off their benzodiazepines. Most patients are excited to start ketamine. I'll say "To maximize your chances that this will work, we should taper your benzodiazepine

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"The message for patients undergoing ketamine-assisted therapy is 'Let go and be open.' Encourage them to be curious without being too literal about the experience, and to avoid jumping too quick to conclusions about the content."

Kyle T. Greenway, MD, MSc

such that the last dose is a couple of nights before your first dose of ketamine.” We published an open-label study of this and did not find significant worsening of depression, anxiety, or even sleep because ketamine is such a powerful treatment by itself. Ketamine also has anticonvulsant effects.

TCPR: How long is an adequate trial of ketamine?

Dr. Greenway: If someone has zero response after four treatments, I would stop. If there is a partial response, I would go to six treatments and reevaluate. Those are some general guides, but we don’t have good data here. I’m referring to ketamine, which is dosed IV 0.5 mg/kg over 40 minutes, approximately twice a week. For esketamine, it is probably similar.

TCPR: If they recover, when do you start to taper off the treatment?

Dr. Greenway: This is where we are in the Wild West. A common protocol is administering ketamine or esketamine twice a week for three to four weeks and then shifting to a maintenance phase with less frequent dosing, such as every two weeks for a few months and then once a month for a few months, and then stopping. The whole taper might take about six months (Kritzer MD et al, *Expert Opin Drug Saf* 2022;21(6):725–732). But at our clinic, we do it differently.

TCPR: How so?

Dr. Greenway: We use a psychotherapy model where ketamine is not the primary treatment. We use it to reduce acute symptoms and increase engagement in psychotherapy. In this Montreal Model we start by setting the stage for behavioral work, then give six doses of ketamine over a month and stop. After that, we typically keep them on other psychiatric medications that they were taking before ketamine, but we use psychotherapy to maintain the response (Garel N et al, *Front Psychiatry* 2023;14:1268832).

TCPR: How do you set the stage for psychotherapy?

Dr. Greenway: The first thing that we do is set goals. We say “Imagine that your depression improves with ketamine. What activities do you see yourself doing to stay well?” Sometimes patients are so focused on symptoms that they forget the basics, like daily routines, sleep hygiene, exercise, and healthy diet. We aim for at least three “SMART” goals, which stands for Specific, Measurable, Actionable, Realistic, and set in Time. A goal might be “I’m going to get out of bed every day at 9 am and take a shower.” Sounds simple, but many of our patients practically live in their beds.

TCPR: What comes next in the Montreal Model?

Dr. Greenway: We always ask people to start psychotherapy. There are many psychological issues involved with treatment-resistant depression, and they are going to need some kind of evidence-based therapy in place to prevent relapse after ketamine. Also, many of our patients are isolated, and the ketamine process is almost guaranteed to generate psychological material that will benefit from a therapeutic process. It ranges from “Wow, I feel better, and I don’t know how to make sense of the last 10 years of my life” to being really disappointed that ketamine did not work the way they had hoped.

TCPR: Does the ketamine experience generate new ways of thinking?

Dr. Greenway: It may, and in our clinic we prepare the patient for this over two to three sessions before starting ketamine. In the first session, we establish the diagnosis and get a snapshot of what a day in their life is like. I ask how they spend their time hour by hour. If they say “I do nothing,” I don’t stop there. My “doing nothing” and somebody else’s “doing nothing” might be totally different. In the second session, we set behavioral goals and start any medication adjustments we need to. In the third visit, we help them prepare psychologically for their first ketamine session.

TCPR: How do you do that?

Dr. Greenway: We often teach a meditation exercise, such as mindfulness or a body scan. We want them to cultivate a sense of curiosity, to be open to their own experience. Sometimes this preparation may take longer. I won’t schedule the first ketamine session until I feel there is a strong collaboration. I want them to have the best chance of success with the treatment.

TCPR: How do you judge collaboration?

Dr. Greenway: I look to see that we’ve set some goals and seen some progress on them. This may not involve another session. After they set goals, I may follow up with a phone call to check on their progress. If they say “I just can’t find the motivation,” I’ll say “Maybe we shouldn’t rush into this.”

TCPR: Tell us about the setting where you deliver ketamine.

Dr. Greenway: It’s actually quite medical, with an IV pump and a machine to monitor heart rate and blood pressure. That’s intentional because this is a medical procedure. But the setting is also very pleasant—we have carpets and plants. While receiving ketamine, patients typically wear a blindfold and listen to music through headphones. We have playlists that create an arc over 40–50 minutes, beginning with calm songs and building in intensity and then returning to calm as people come back to reality. You can find it on Spotify (search for Montreal Ketamine Clinic). We have several playlists—jazz, classical, electronic—and let the patient choose. In later sessions, we might invite them to make their own playlists. The main thing is it should be instrumental, or at least not have intelligible lyrics. We want their imagination to flow.

TCPR: Is the patient alone during the treatment?

Dr. Greenway: No. There is a therapist in the room, and the patient may turn to them for support or guidance, though typically they are not interacting much during the infusion. Afterward, as they come out of it, they talk about what happened.

TCPR: What sort of experiences do patients have?

Dr. Greenway: Powerful stuff often comes up—emotional, dream-like, even spiritual. It might also

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simply be fear—in all the trials there is usually a rate of 1%–5% of people dropping out due to anxiety or panic. We discuss this possibility in advance, but we avoid pathologizing it with words like “dissociation.” The message is to “let go and be open.” In other words, be curious without being too literal about the experience. Don’t jump too quick to conclusions about the content.

TCPR: What happens in the therapy sessions that follow the ketamine treatment?

Dr. Greenway: The therapy we use follows the acceptance and commitment therapy model. Briefly, it involves teaching patients to feel their emotions, to diffuse their thoughts, and to change their behavior. By “diffuse,” I mean to gain some detachment from their thoughts, similar to what happens in mindfulness. They learn to view their own thoughts as phenomena in their mind, or as words on a screen, rather than “the truth.”

TCPR: Is it important that they set goals that align with their values?

Dr. Greenway: I think values are important in behavioral therapy, but it’s hard for people with severe depression to get in touch with them. So my patients often choose very basic goals, things that are generally good for anyone, like walking in nature, socializing, or brushing their teeth every day. Of course, there is a value in those goals, which is taking care of themselves. Starting those routines can build self-esteem, helping to chip away at the guilt and worthlessness that are part of depression.

TCPR: Back to the collaboration, it’s almost like you’re asking them to care about themselves before they start ketamine.

Dr. Greenway: That is the implicit message. We need to communicate “Ketamine can help, but it won’t fix you. Eventually you’re going to have to fix you.” That is a hard message to deliver, and it takes a lot of trust and kindness. It may be better conveyed implicitly, saying things like “Can we find three small changes in your life that we can work on together?” You’re engaging the patient to make changes in their life without shaming them for spending all day in bed, for instance.

TCPR: Thank you for your time, Dr. Greenway.

Dr. Greenway’s interview is continued in the June 10, 2024, episode of The Carlat Psychiatry Podcast.



Off-Label Strategies for Common Psychiatric Conditions

Continued from page 4

2019;33(2):167–176). Patients at risk for suicide are good candidates. Other predictors of a good response to lithium augmentation of antidepressants include severe depression, high recurrence (>3 past episodes), significant weight loss, psychomotor retardation, and a family history of bipolar disorder or of lithium response (Taylor et al, 2020).

Lithium can be added to any antidepressant, although it carries a very low risk of serotonin syndrome when used with serotonergics or monoamine oxidase inhibitors. Start with 150–300 mg at night and raise by 300 mg every three to seven days toward a target dose of 900 mg QHS (or 450 mg if the patient is elderly or has drug interactions). Then wait five days and check the trough level in the morning, aiming for a serum level of 0.5–0.8 mEq/L (for the elderly, lower the target level to 0.4–0.7 mEq/L for age 60–79 years and 0.4–0.6 mEq/L for age ≥80 years).

CARLAT VERDICT

For antidepressant augmentation, the off-label lithium is a close competitor to the atypical antipsychotics and may be preferable for patients at risk for suicide.

Ketamine vs Esketamine

In 2019, the FDA approved esketamine (Spravato) for treatment-resistant depression and depression with suicidality, but some would argue they got the wrong drug.

Compared to esketamine, the unapproved ketamine was twice as likely to bring patients to response or remission, and less likely to lead to dropouts, in an analysis of 24 trials (Bahji A et al, *J Affect Disord* 2021;278:542–555). Ketamine contains esketamine and its mirror-image enantiomer arketamine in a 50/50 racemic mix. Since ketamine is generic, the only profitable path to FDA approval was by copyrighting and testing one of those enantiomers, which Janssen did with esketamine.

The other enantiomer, arketamine, is under development through Perception Neuroscience, and it’s this enantiomer that may explain ketamine’s superior effect. Animal data suggest arketamine is safer and more effective than esketamine, with greater antidepressant effects and lower abuse potential. Another explanation involves the mode of delivery. Ketamine is usually delivered IV, leading to greater absorption and higher plasma levels than the intranasal esketamine.

Although the available data favor ketamine over esketamine, none of this information is based on direct, head-to-head comparisons. In fairness, esketamine’s trials were designed in a way that tends to dampen effect size (ie, they were larger and more rigorous).

What about oral ketamine? This form is prescribed at some clinics as a lozenge, but it is not as strong an off-label contender as the IV form. Fewer than 10% of the ketamine trials tested the oral form. Ketamine has low bioavailability, so the oral version may not be reliably absorbed. Oral ketamine also raises the risk of diversion. Ketamine and esketamine are Schedule III controls, and the FDA requires patients to take esketamine under supervision. Practitioners would be wise to follow that same standard when using ketamine off-label.

CARLAT VERDICT

Ketamine may be more effective than esketamine. For patients who need this level of care, both are reasonable options, and the choice often comes down to pragmatics. Ketamine is less costly, but also less likely to be covered by insurers.

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Autism

Although there are no FDA-approved medications for autism, two antipsychotics—aripiprazole (5–15 mg/day) and risperidone (0.5–3 mg/day)—are approved for *irritability* associated with autism in children (5–17 years old). Both antipsychotics improved irritability with a large effect size. They also reduced hospitalization rates. Between the two, aripiprazole was better tolerated (Fung LK et al, *Pediatrics* 2016;137 Suppl 2:S124–S135).

However, antipsychotics carry significant risks, particularly in children who are more vulnerable to their metabolic effects. For irritability in autism, behavioral and family therapy are first line, and antipsychotics are best reserved for short-term management of severe aggression. For less severe aggression, there are safer options with controlled-trial evidence. These include the ADHD medication clonidine (0.1–0.3 mg/day, usually delivered by transdermal patch), and two supplements: omega-3 fatty acids (600–1500 mg/day of EPA + DHA omega-3) and the glutamatergic antioxidant N-acetylcysteine (NAC, 500–2700 mg/day) (Fung et al, 2016).

CARLAT VERDICT

No medications target the core symptoms of autism. For problematic aggression, start with psychotherapy approaches, clonidine, omega-3, or NAC. Reserve the FDA-approved antipsychotics for severe aggression where the benefits outweigh the risks.

Binge Eating Disorder

Lisdexamfetamine (Vyvanse) is the sole FDA-approved agent here, with specific approval for moderate to severe binge eating disorder (BED) in adults. On the surface, there is not much to argue with. Lisdexamfetamine 50–70 mg/day brought about a meaningful difference in three large trials (Fornaro M et al, *Neuropsychiatr Dis Treat* 2016;12:1827–1836). Although patients were twice as likely to discontinue lisdexamfetamine as they were to discontinue placebo, the drug did not cause serious harm and had a reasonable safety profile in a one-year extension study.

On the other hand, amphetamines like lisdexamfetamine can worsen many of the disorders that commonly co-occur with BED, particularly bipolar, borderline, psychotic, and substance use disorders (Welch E et al, *BMC Psychiatry* 2016;16:163). Patients with a history of those disorders were excluded from the trials, as were those with hypertension, cardiac disease, or significant symptoms of any comorbid psychiatric disorder.

Around one in five patients with bipolar disorder have BED, particularly those with emotional reactivity, impulsivity, and atypical depression (ie, the depression that raises appetite) (Boulanger H et al, *J Affect Disord* 2018;225:482–488). For these patients, topiramate (150–600 mg/day) is a safer option. For patients with other comorbidities, where an antidepressant may be safe but an amphetamine ill advised, several antidepressants have evidence in BED: duloxetine (60–120 mg/day), fluoxetine (40–60 mg/day), and sertraline (100–200 mg/day) (Reas DL and Grilo CM, *Expert Opin Pharmacother* 2015;16(10):1463–1478). For all patients with BED, psychotherapy is worth considering first.

CARLAT VERDICT

Psychotherapy is first line for BED. The FDA-approved lisdexamfetamine is appropriate for pure BED, but a nonstimulant is often preferable for patients with major psychiatric comorbidities.

Tardive Dyskinesia

The vesicular monoamine transporter type 2 (VMAT2) inhibitors deutetabenazine (Austedo) and valbenazine (Ingrezza) were approved for tardive dyskinesia (TD) in 2017 through the FDA's accelerated pathway. They are an improvement over the original VMAT2 inhibitor, tetrabenazine, which carries a risk of inducing depression and suicidality.

Although these FDA-approved options are first line for TD, they come with problems that will send many to second-line options. They cost around \$80,000 per year, and many do not respond to them, based on their number needed to treat of 4–7 (Solmi M et

al, *Drug Des Devel Ther* 2018;12:1215–1238). In that case, amantadine (100–400 mg/day) and levetiracetam (Keppra, 500–3000 mg/day) are reasonable alternatives.

Amantadine is a glutamatergic medication that is approved for dyskinesias in Parkinson's disease. It has been used since the early 1970s for TD and ranks just below VMAT2 inhibitors in treatment guidelines for TD, with support from three controlled trials (Artukoglu BB et al, *J Clin Psychiatry* 2020;81(4):19r12798). It also reduced antipsychotic weight gain in five controlled trials, where it had additional benefits in negative symptoms of schizophrenia (Zheng W et al, *J Clin Psychopharmacol* 2017;37(3):341–346). The main side effect is insomnia, although rarely it can induce hallucinations.

Levetiracetam (Keppra) is an anti-convulsant that modulates dopamine transmission. Its ability to improve dyskinesias in Parkinson's disease led to open-label studies in TD that were confirmed by a small controlled trial (Artukoglu et al, 2020). Somnolence and dizziness are its main risks, although rarely it can cause neuropsychiatric symptoms from aggression to depression. While most anticonvulsants cause cognitive dulling, levetiracetam has potential procognitive effects, and it did improve negative symptoms of schizophrenia in a controlled trial (Behdani F et al, *Int Clin Psychopharmacol* 2022;37(4):159–165).

In some situations, it is better to switch or discontinue the antipsychotic to address TD. Clozapine does not cause TD and is a good option for patients with schizophrenia who have not responded well to two antipsychotic trials. In mood disorders, antipsychotics are often used as augmentation, and they can be tapered off in favor of relying on other therapies for prevention.

CARLAT VERDICT

The FDA-approved options for TD are first line, but their cost will steer many toward the off-label amantadine and levetiracetam.

Antipsychotic Weight Gain

The FDA has approved only one medication to reduce weight gain on antipsychotics. Lybalvi is a combination of the opioid antagonist samidorphan with olanzapine, and in my view, it is not first line.

Although samidorphan prevented weight gain, it did not make a dent in the more meaningful markers of metabolic syndrome. Metformin, in contrast, improved insulin sensitivity, fasting glucose, and triglycerides, as well as hyperprolactinemia and cognition (Zheng W et al, *J Clin Psychopharmacol* 2015;35(5):499–509; Zheng W, *J Psychopharmacol* 2017;31(5):625–631). Compared to Lybalvi, which was only tested in nonobese patients, metformin has support from a larger and broader body of research. APA guidelines recommend it first line for adverse effects of antipsychotics.

Metformin is well tolerated. Nausea and diarrhea are the most common side effects and improve by taking the medication with food or using the extended-release form. Very rarely, metformin can cause lactic acidosis or vitamin B₁₂ deficiency. Its benefits are greater when started early in the course of antipsychotic therapy before weight gain gets out of control.

With over a dozen randomized controlled trials for antipsychotic weight gain, metformin is the

best-studied agent in this area but lacks FDA approval for any kind of weight loss. Its dominance is being challenged by the glucagon-like peptide-1 (GLP-1) receptor agonists, three of which are FDA approved for weight loss in obesity (see the table “Metformin and the GLP-1 Agonists for Antipsychotic Weight Gain” on page 4). Specifically, liraglutide, semaglutide, and tirzepatide are approved for patients with a BMI ≥ 30 kg/m². If the patient has medical complications of obesity (eg, hypertension, type II diabetes, or dyslipidemia), a BMI ≥ 27 kg/m² is allowed.

Two GLP-1 agonists—liraglutide and semaglutide—have support from case series in antipsychotic weight gain, although only liraglutide has a randomized controlled trial there. After adjusting for placebo, liraglutide led to a 12-pound weight loss over three months in that study, which tested the drug in 97 patients on olanzapine or clozapine with prediabetes and a mean BMI of 34 kg/m². By comparison, metformin brought about a seven-pound weight loss in studies of a similar duration. Like metformin, liraglutide led to improvements in metabolic variables: glucose tolerance, blood pressure, and LDLs (Larsen JR et al, *JAMA Psychiatry* 2017;74(7):719–728).

The high cost of the GLP-1 agonists has slowed their adoption in psychiatry, but a generic liraglutide is slated for

release in 2024. Both drugs are delivered by subcutaneous injection, although their half-lives lend an advantage to the weekly semaglutide over the daily liraglutide. The sole head-to-head comparison of these two also favors semaglutide, which brought about a 16% vs 6.4% reduction in body weight in a 68-week randomized controlled trial of 338 obese patients without diabetes (sponsored by semaglutide’s manufacturer) (Rubino DM et al, *JAMA* 2022;327(2):138–150).

The most common side effects with GLP-1 agonists are nausea, diarrhea, and constipation. The medications slow gastric emptying, and the FDA recently placed a warning on semaglutide for intestinal blockage (ileus). Common warnings across the -glutides are thyroid cancer, acute kidney injury, gallbladder disease, and pancreatitis.

Metformin and GLP-1 agonists can be safely combined with Lybalvi, but the two antidiabetic medications (metformin and GLP-1 agonists) bring an additive risk of hypoglycemia if used together.

CARLAT VERDICT

Metformin and the -glutides have broader benefits than the FDA-approved Lybalvi. Start metformin early for prevention of weight gain. For patients whose BMI rises above 30 kg/m² (or 27 kg/m² with medical complications), the GLP-1 agonists are FDA approved and appropriate to use with antipsychotics.



Research Updates IN PSYCHIATRY

ANTIDEPRESSANTS

STAR*D Reanalysis Causes New Debate Over Antidepressant Efficacy

Alex Evans, PharmD, MBA. Dr. Evans has no financial relationships with companies related to this material.

REVIEW OF: Pigott HE et al, *BMJ Open* 2023;13:e063095

STUDY TYPE: Reanalysis of an open-label, randomized, rater-blinded clinical trial

When it comes to antidepressant efficacy, we often hang our hats on the 67% cumulative remission rate reported in the 2006 landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. But a new reanalysis has sparked debate over those results.

STAR*D was funded by the National Institute of Mental Health. It included 4,041 patients ages 18–75 who scored >14 on the Hamilton Rating Scale for Depression (HRSD). All patients started on citalopram. If needed, they progressed through four treatment levels involving cognitive behavioral therapy and 14 pharmacologic strategies, with 12 weeks at each level (plus two more weeks if they

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Research Updates

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were close to remission). In the spirit of a real-world study, STAR*D included patients with comorbid medical and psychiatric conditions.

STAR*D's primary outcome was remission, defined by <8 on the blinded HRSD. The secondary outcome was response (>50% reduction in HRSD). Although nonblinded assessments like the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) were not identified as outcomes, investigators used the QIDS-SR as a primary outcome in the published reports. 931 patients who didn't meet criteria for depression were included in the level 1 (citalopram) analysis. 370 patients dropped out after their first clinic visit and should have been included but weren't, and 125 patients already in remission were included in analysis for the next level of treatment.

These deviations from the study protocol likely inflated the results, so researchers in this study reanalyzed STAR*D according to the protocol. It didn't spell out what to do with patients who dropped out without an exit HRSD, so researchers calculated two remission rates: one that assumed none of these patients achieved remission, and another that counted patients with an exit QIDS-SR <6 as in remission.

Under both scenarios, antidepressant efficacy fell below the 67% cumulative remission rate originally reported. The new remission rates were 35% when only patients with an exit HRSD score were included, and 41% when those with a QIDS-SR <6 were added.

CARLAT TAKE

The remission rate in STAR*D depends on how the data are analyzed. Using the original protocol results in cumulative remission rates that are about half (35%–41%) of what was originally reported (67%). When analyzed according to the original protocol, STAR*D showed modest remission rates of about half (35%–41%) of what was originally reported (67%).

ANXIETY DISORDERS

Memantine for Trichotillomania and Excoriation Disorder

Sarah Azarchi, MD. Dr. Azarchi has no financial relationships with companies related to this material.

REVIEW OF: Grant JE et al, *Am J Psychiatry* 2023;180(5):348–356

STUDY TYPE: Randomized double-blind placebo-controlled trial

Pharmacologic options for trichotillomania (hair-pulling) and excoriation (skin-picking) disorder are extremely limited. Selective serotonin reuptake inhibitors, antipsychotics, N-acetylcysteine (NAC), naltrexone, and modafinil have all been tried but have not yielded consistent support from controlled trials. Glutamate plays a role in motor habits, and the glutamatergic modulator NAC improved trichotillomania in a small randomized controlled trial by Grant and colleagues. In the current study, Grant's team tested memantine, a glutamate modulator and N-methyl-D-aspartate receptor antagonist that has been FDA approved only for the treatment of Alzheimer's disease.

In this randomized, placebo-controlled, double-blind trial, 100 people with trichotillomania (53%), excoriation disorder (43%), or both (4%) received treatment over eight weeks. Most of the patients (86%) were women with an average age of 31.4 years. A total of 55 participants received memantine (10 mg/day for one week, then 20 mg/day for the remainder of the study) while the placebo group (n=45) received identical capsules for the same period. Some participants in both groups were in concurrent psychotherapy (including cognitive behavioral therapy) and/or receiving psychotropic medication. They were excluded only if there had been a change in treatment in the preceding three months.

Treatment with memantine demonstrated superior outcomes at eight weeks compared to placebo, as indicated by significant improvement in scores on the National Institute of Mental Health's Trichotillomania Symptom Severity Scale (60.5% experienced severity improvement in the memantine group vs 8.3% in the placebo group, Fisher's exact test $p < 0.0001$). The number needed to treat for improvement

was 1.9. No serious adverse events were reported in either group. Two participants in the memantine group dropped out due to dizziness.

CARLAT TAKE

While the results are encouraging for memantine in trichotillomania and excoriation, we'll add a note of caution as many treatments have failed after showing initial promise in these disorders.

PSYCHOPHARMACOLOGY

Does Haloperidol Improve Hospitalization or Mortality in Delirium?

Jeremy Mills, DNP, PMHNP-BC. Dr. Mills has no financial relationships with companies related to this material.

REVIEW OF: Andersen-Ranberg NC et al, *N Engl J Med* 2022;387(26):2425–2435

STUDY TYPE: Randomized double-blind placebo-controlled trial

Antipsychotics are often used for agitation in delirium, but recent studies have called their efficacy into question and some practice guidelines do not recommend them (Devlin JW et al, *Crit Care Med* 2018;46(9):e825–e873). This study looked at whether haloperidol improved meaningful long-term outcomes.

This four-year, double-blind study randomized 1,000 ICU patients in five European countries to haloperidol or placebo. After diagnosing delirium through a validated measure, researchers administered 2.5 mg of IV haloperidol or placebo three times daily. Additional PRN doses, up to a maximum daily dose of 20 mg, were given for recurring symptoms. IV placebo was dosed at a similar rate, and doses were stopped when delirium resolved. Patients remained in the same study arm across any subsequent admissions. The primary outcome was days alive and out of the hospital after three months. Secondary outcomes included

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CME Post-Test

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1. What is a key factor in promoting positive psychiatric outcomes, according to Dr. Mintz (LO #1)?
 - a. Prescribing multiple medications simultaneously
 - b. Encouraging patients to rely solely on medication for recovery
 - c. Strengthening the therapeutic alliance
 - d. Minimizing patient involvement in treatment decisions

2. Which SSRI is recommended first-line for PTSD due to its efficacy and side effect profile, despite not being FDA approved (LO #2)?
 - a. Sertraline
 - b. Paroxetine
 - c. Fluoxetine
 - d. Venlafaxine

3. Which accurately reflects therapy after ketamine treatment in Dr. Greenway's practice (LO #3)?
 - a. Therapy sessions center on guided imagery, building from the ketamine experience
 - b. Patients set a psychotherapy end date that coincides with the end of ketamine treatment
 - c. Therapy sessions following ketamine treatment utilize the acceptance and commitment therapy model
 - d. Ketamine treatment replaces the need for ongoing therapy sessions

4. What was a limitation in the original STAR*D study (LO #4)?
 - a. Biased views
 - b. Deviations from the study protocol
 - c. Insufficient sample size
 - d. Enrollment of subthreshold cases

5. What does Dr. Mintz recommend to address patient ambivalence toward treatment (LO #1)?
 - a. Focusing on medication management
 - b. Exploring psychological factors that influence the patient's readiness for change
 - c. Identifying external consequences and rewards
 - d. Adopting a directive approach

6. For binge eating disorder with major psychiatric comorbidities, which of the following is ill advised (LO #2)?
 - a. Duloxetine (Cymbalta)
 - b. Lisdexamfetamine (Vyvanse)
 - c. Sertraline (Zoloft)
 - d. Fluoxetine (Prozac)

7. Which is a recommended approach for combining ketamine with therapy in treatment-resistant depression (LO #3)?
 - a. Initiate ketamine infusions during the initial appointment
 - b. Attempt to discontinue all psychiatric medications before starting ketamine treatment
 - c. Initiate ketamine treatment before behavioral change occurs
 - d. Establish collaborative goal-setting sessions and behavioral therapy before initiating ketamine treatment

8. In a study by Grant et al, which psychotropic showed superior outcomes compared to placebo in the treatment of trichotillomania and excoriation disorder (LO #4)?
 - a. N-acetylcysteine
 - b. Modafinil
 - c. Memantine
 - d. Naltrexone

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Research Updates

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mortality; days without coma, delirium, or ventilator; serious adverse reactions; and use of restraints or rescue medications for delirium (including other antipsychotics).

There were no statistically significant differences in any outcomes. Adverse reactions were similar between the two groups, although there was a nonsignificant trend toward greater QT prolongation with haloperidol.

Although the researchers did not assess direct improvement in symptoms of delirium, the lack of a difference in the use of rescue medications or restraints raises doubts about haloperidol's efficacy. A meta-analysis of 11 randomized trials failed to find a difference in "days without delirium" on haloperidol (Andersen-Ranberg NC et al, *Crit Care* 2023;27(1):329). Also, the results may not fully generalize to the US population. European ICUs have comparatively lower rates of mental illness and use sitters more than restraints. In this study, patients who were already on antipsychotics were excluded, and only 1,000 of the 1,738 screened patients were included. The doses of haloperidol used were also comparatively low.

CARLAT TAKE

This study adds to mounting evidence against antipsychotics in ICU delirium. For mild delirium, nonpharmacologic measures and sleep regulation have better support as first-line interventions.



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