# THE CARLAT REPORT PSYCHIATRY

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**Chris Aiken, MD**
**Editor-in-Chief**


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## IN THIS ISSUE

*Focus of the Month:*
**Esketamine**



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

1. Evaluate the safety and efficacy of esketamine as an interventional therapy for treatment-resistant depression.
2. Assess and treat tardive dyskinesia in patients on antipsychotics.
3. Identify the optimal duration of antipsychotic augmentation in mood disorders.
4. Summarize some of the current research on psychiatric treatment.

# How to Treat Tardive Dyskinesia


*Chris Aiken, MD. Editor-in-Chief of* The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*


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

*Your patient is a 56-year-old male who recovered from a difficult-to-treat depression 4 years ago after quetiapine was added to his citalopram. As he talks, you notice that his fingers are tapping in a rapid, random pattern and his feet are wiggling. When questioned, he explains, "I just do that when I'm anxious." Should you stop the antipsychotic, start one of the new medications for tardive dyskinesia, or let it pass?*

In 2017, the first FDA-approved medications for tardive dyskinesia (TD) came out: valbenazine (Ingrezza) and deutetrabenazine (Austedo). They aren't exactly new—both are derivatives of tetrabenazine, which has been used for TD since the 1970s—nor are they the only options for TD. I've been involved in TD research and education for 2 decades, and in this article I'll describe how I manage this insidious condition.

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**Highlights From This Issue**

Nolan Williams discusses when to use esketamine, TMS, and ECT, and addresses doubts that have surrounded esketamine's release, from neurotoxicity to addiction and withdrawal.

Ingrezza and Austedo are compared for TD, along with 8 off-label options.

When adjunctive antipsychotics bring unwanted side effects, it may be safe to taper off after 6 months of recovery in mood disorders.

Q&A With the Expert

# Getting Uncomfortable With Esketamine
## Nolan Williams, MD


*Director of the Brain Stimulation Lab and Interventional Psychiatry Clinical Research Program; Assistant Professor of Psychiatry at Stanford University, CA.*


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

*Esketamine (Spravato) was approved for treatment-resistant depression in 2019. In this interview, Dr. Williams (who has no relationship with Janssen Pharmaceuticals, Inc) addresses some lingering doubts that have been raised about the medicine.*

**TCPR: Where does esketamine fit in the list of interventional therapies for depression, like repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT)?**

**Dr. Williams:** For my practice, right now ketamine and esketamine have two roles. One is for people who don't respond to conventional rTMS—that is, rTMS with the FDA-approved methods—and either cannot or don't want to try a course of ECT. About half of people who try conventional rTMS don't benefit from it, so this is a fair number of people we're talking about. The second is in emergency settings, where there's a need for rapid relief of suicidality. For example, it might be useful with a patient who needs a sitter in the ER because of severe suicidal urges.

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**Spontaneous dyskinesias: The other TD**

History is important here. Long before the antipsychotics arrived, psychiatrists were describing dyskinesias that looked identical to TD in patients with schizophrenia. Like TD, these "spontaneous dyskinesias" get worse with age, with rates of up to 40% in antipsychotic-naïve patients after age 60. Unlike TD, they get worse during psychotic flare-ups and improve with antipsychotic therapy. Spontaneous dyskinesias are unheard of in mood disorders, although they are seen in schizotypal personality disorder and in close relatives of patients with schizophrenia.

**TD in the antipsychotic era**

TD was first recognized in the early 1960s. By the 1970s, it had become such a problem that it nearly halted the development of new antipsychotics. Clozapine offered hope. It was, and remains, the only antipsychotic that does not cause TD. Research poured into developing a safer version of clozapine, which is how we got the atypical antipsychotics. Banking on that history, many thought these new drugs would put an end to TD. Some of the early cases of TD on atypicals were even dismissed as spontaneous dyskinesias. That explanation no longer held up when TD started appearing in patients with mood disorders on atypical antipsychotics.

It is now accepted that atypical antipsychotics can cause TD, though some continue to claim that various atypicals (eg, aripiprazole, quetiapine) are free of risk. So far, those arguments have not held up to the data. TD is less common and less severe with atypicals than it is with conventional antipsychotics. The annual incidence of TD is 2.6% on atypical antipsychotics, which translates to a risk of 20% after 10 years. For conventional antipsychotics, that risk is double. However, the elderly have the same annual incidence (5.2%) for both antipsychotic classes (Carbon M et al, *World Psychiatry* 2018;17(3):330–340; Correll CU and Schenk EM, *Curr Opin Psychiatry* 2008;21(2):151–156).

**Diagnosis of TD**

Mild cases of TD can be socially embarrassing, and severe cases can make it painful to eat, speak, or even breathe. Writhing movements of the mouth, eyes, hands, and feet are the most common manifestations. Patients may not notice them or may dismiss them as "nervous habits." Relatives are often better observers.

When patients are on an antipsychotic, I'll scan their face, hands, and feet at every visit for abnormal movements. If I see any, I'll complete the Abnormal Involuntary Movement Scale (AIMS) (www.cqaimh.org/pdf/tool_aims.pdf). It's recommended to complete an AIMS 1–2 times a year for patients on an antipsychotic, and insurers require it to authorize medications for TD. If you don't do the full scale, then perform these basic checks:

1. **Tongue and face:** The tongue is a visible muscle, so you may catch early signs of TD there. Ask the patient to open their mouth wide with their tongue at rest. Does it lie still or squirm and writhe uncontrollably?
2. **Hands and feet:** Have the patient sit with their legs apart and their hands on their knees. Are their feet squirming? Toes flexing up and down? Do their fingers make random tapping motions ("piano player hands")?
3. **Reinforcement:** If you did not see any movements with steps 1–2, repeat them while having the patient perform a distracting task, such as the patient writing their name in the air. This can "reinforce" or bring out any undetected TD.

**Management of TD**

*Step 1: Prevention*

Prevention starts by minimizing antipsychotics in patients who are at risk. Among the risk factors, age over 50 is the strongest; others include mood disorders, history of substance abuse, brain injury, diabetes, HIV+, female gender, African American race, and presence of extrapyramidal side effects (EPS) (Correll CU et al, *J Clin Psych* 2017;78(8):1136–1147).

Once patients are on an antipsychotic, try to minimize the dose and duration. Antipsychotic discontinuation may not be possible in schizophrenia, but in mood disorders it is more feasible than industry-supported trials would have us believe (see page 6).

*Step 2: Taper off*

When the first signs of TD appear, open the discussion about the risks and benefits of the antipsychotic. If discontinuing, go slowly, lowering the dose every 2–4 weeks. The dyskinesias may worsen at first because higher antipsychotic doses can mask TD, and *withdrawal dyskinesias* may occur for a few months after the antipsychotic is stopped. Although TD can be permanent, 30%–50% of cases resolve with discontinuation.

*Step 3: Switch*

If discontinuation is not successful, switching may help. Clozapine is the only antipsychotic that does not cause TD, but it has other risks that may preclude its use, especially in mood disorders. Aripiprazole (Abilify) comes in second place, followed by olanzapine (Zyprexa), according to a meta-analysis of 57 head-to-head trials (Carbon M et al, *World Psychiatry* 2018;17(3):330–340). Surprisingly, quetiapine (Seroquel) had the highest risk in that study, although it is often touted as the preferred antipsychotic

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How to Treat Tardive Dyskinesia

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for patients with TD. Like clozapine, quetiapine has a low rate of EPS and low levels of $D_2$ occupancy, qualities that—in theory—predict a low risk of TD.

*Step 4: $VMAT_2$ inhibitors*

When tapering and switching do not work, I'll attempt to treat the TD, and the FDA-approved $VMAT_2$ inhibitors are first line: valbenazine (Ingrezza) and deutetrabenazine (Austedo). Though released in 2017, their history dates back to the early 1970s when their predecessor tetrabenazine was first used to treat TD. Tetrabenazine never caught on because it had a tendency to cause depression and suicidality, so the molecule was adjusted to reduce that risk. So far, the modifications have worked, and valbenazine and deutetrabenazine have not caused significant depression in trials involving mood and psychotic disorders. Deutetrabenazine, however, does carry a black box warning for depression and suicidality in Huntington's disease, for which it is also FDA approved. (See "Treatments for Tardive Dyskinesia" table below.)

The $VMAT_2$ inhibitors work by reducing dopamine hypersensitivity, which is one of several mechanisms thought to underlie TD. These medications don't worsen psychosis. In fact, earlier $VMAT_2$ inhibitors like reserpine have successfully treated psychosis (Remington G et al, *J Clin Psychopharmacol* 2012;32(1):95–99).

In clinical trials, the response rates were 1 in 4 for valbenazine and 1 in 7 for deutetrabenazine (≥ 50% response). However, the trials were not head-to-head studies, so these aren't fair comparisons. Instead, more practical considerations may favor valbenazine. It is dosed once a day, while deutetrabenazine is dosed twice a day and must be taken with food (Solmi M et al, *Drug Des Devel Ther* 2018;12:1215–1238).

The $VMAT_2$ inhibitors take 4–6 weeks to work, and if they do work they should be continued as long as the antipsychotic is onboard. Otherwise, the TD tends to return within a month of discontinuation.

*Step 5: Second-line agents*

Dopaminergic hypersensitivity is not the only mechanism behind TD, and there are second-line agents that address other pathways. The best studied are the glutamate antagonist amantadine, which is FDA approved for dyskinesias in Parkinson's disease, and the neuroprotective herb ginkgo. These are each supported by 3–4 small, randomized controlled trials (RCTs). The others in the table are supported by 1–2 RCTs or, in the case of vitamin E, a mix of positive and negative studies (Lin CC and Ondo WG, *J Neurol Sci* 2018;389:48–54).

I usually start with amantadine or ginkgo. After that, levetiracetam (Keppra) is one I've seen success with. Many of the options in the table address other psychiatric conditions, and it's those comorbidities that often guide the selection.

One treatment to avoid is benztropine (Cogentin). Although useful for parkinsonian side effects, its anticholinergic effects can make TD worse (Citrome L, *J Neurol Sci* 2017;383:199–204).

**TCPR VERDICT:** It's easy for patients and providers to miss the mild presentations of TD that creep up with atypical antipsychotics. TD is treatable, but the FDA-approved options may only help 15%–25% of patients and are extremely expensive. Off-label treatments like amantadine, ginkgo, and levetiracetam are worth trying when the symptoms are significant and the antipsychotic can't be removed.

***To learn more, listen to our 1/20/20 podcast, "Tardive Dyskinesia: How to Get Through Prior Auths and When to Go Off-Label."*** Search for "Carlat" on your podcast store.

**Treatments for Tardive Dyskinesia**

| | Dose | Risks | Notes |
|---|---|---|---|
| **First Line** | | | |
| **Deutetrabenazine (Austedo)** | 6 mg BID for 1 week, then raise based on response by 3 mg BID every week; max 24 mg BID; take with food | QTc prolongation, insomnia, nasopharyngitis, possible depression and suicidality | These usually need to be ordered through a specialty pharmacy ($6,000/month) |
| **Valbenazine (Ingrezza)** | 40 mg QHS for 1 week, then 80 mg QHS with or without food | QTc prolongation, sedation, possible depression and suicidality | |
| **Second Line** | | | |
| **Amantadine** | 100–400 mg, divided TID | Hallucinations, livido reticularis (skin discoloration), anticholinergic effects | Potential benefits in antipsychotic weight gain, depression, OCD, ADHD, and irritability |
| **Ginkgo extract EGb-761** | 240 mg QD | No serious risks | Tebonin brand, $2/day on Amazon |
| **Third Line** | | | |
| **Branched amino acids** | Valine, isoleucine, and leucine in 3:3:4 ratio (222 mg/kg TID) | Possibly weight gain or diabetes | Previously sold as Tarvil; can be obtained at compounding pharmacy; only studied in men |
| **Clonazepam** | 1–4.5 mg divided BID or TID | Dependence/abuse, falls, memory impairment | |
| **Levetiracetam (Keppra)** | 500–2,000 mg QHS | Fatigue, dyscoordination; psychiatric side effects are fairly common (eg, depression, irritability, psychosis) | |
| **Melatonin** | 10 mg QHS (lower doses did not work) | Fatigue | 3–5 mg QHS reduces antipsychotic weight gain |
| **Vitamin B6** | 400–1,200 mg QD | Dose-dependent neuropathy | Also treats akathisia and tremor in same dose |
| **Vitamin E** | 1,200 IU QD | Hemorrhagic stroke, prostate cancer | Useful only in mild cases where it has preventative benefits |

Expert Interview

Continued from page 1

**TCPR: How is esketamine different from ketamine?**

**Dr. Williams:** Ketamine is made up of 2 isomers: (R)-ketamine (aka arketamine) and (S)-ketamine (aka esketamine). In this interview, I'll use the phrase "ketamine/esketamine" when referring to both compounds. These are like right- and left-handed scissors: They look the same, but if you're right handed and have ever tried to use left-handed scissors, you know they're not. So we can't completely translate the ketamine findings to esketamine, especially since there's evidence that the other isomer—arketamine—may be the more potent one. In animal models of depression, arketamine has more potent and longer-lasting antidepressant effects, less rewarding effects, less neurotoxicity, and fewer side effects (Yang C et al, *Transl Psychiatry* 2015;5(9):e632). It's too early to say how ketamine and esketamine compare clinically, but a head-to-head study is underway that will shed light on that (Correia-Melo FS et al, *Medicine* (Baltimore) 2018;97(38):e12414). Ketamine also has an active metabolite—norketamine—so it's a complex drug.

**TCPR: Is anyone developing arketamine for depression?**

**Dr. Williams:** Yes. Perception, a Japanese pharmaceutical company, owns the patent and just started clinical trials in 2019. Janssen owns the esketamine patent, and the patent for ketamine is long expired, which is why these companies are pursuing the isomers.

**TCPR: You alluded to some risks with esketamine. What would steer you away from it?**

**Dr. Williams:** Ketamine/esketamine may have an abuse liability. There have been cases where patients get exposed to ketamine in an office setting and then start to order it off the internet. One academic center even shut down its ketamine program because of concerns about drug-seeking behavior (Newport DJ et al, *Depress Anxiety* 2016;33(8):685–688). These problems were not reported in the esketamine trial, but the investigators screened out the kinds of patients who are at risk for abuse. On balance, ketamine has some promising data as a treatment for addictions, like cocaine and alcohol (Dakwar E et al, *Mol Psychiatry* 2017;22(1):76–81). So this could go either way.

**"Ketamine and esketamine may have an abuse liability. That's why I'm more comfortable with single-dose treatment of IV ketamine, like the way it might be used in the ER for suicidality. We also have more data on the one-time use because that's how most of the ketamine studies were done. It's analogous to single-dose opioid administration for acute pain: If someone breaks their leg, they go to the ER and they'll probably get an opiate, but that one-time use is unlikely to lead to addiction."**

Nolan Williams, MD

**TCPR: And I guess that abuse potential is greater when we move toward long-term use.**

**Dr. Williams:** That is possible, although more studies are necessary. That's why I'm more comfortable with single-dose treatment of IV ketamine, like the way it might be used in the emergency room for suicidality. That's analogous to single-dose opioid administration for acute pain: If someone breaks their leg, they go to the ER and they'll probably get an opiate, but that one-time use is unlikely to lead to addiction. We also have more data on the one-time use because that's how most of the ketamine studies were done.

**TCPR: What if the patient is discharged from the emergency room? Could the suicidality return when the dose wears off in a few days?**

**Dr. Williams:** You'd want that patient followed closely like in a partial hospital program or even a ketamine/esketamine treatment center. We deal with the same issue with hospitalization. Many patients are hospitalized for 3 days, or even 1 day, and discharged as soon as their suicidal thinking resolves. Those first few months after hospital discharge are a high-risk period for suicide. The question you're raising is how long the benefits of single-dose IV ketamine or intranasal esketamine will last. A separate issue is whether there's a withdrawal phenomenon when ketamine/esketamine wears off. I'm not so worried about that after one dose, but it is a concern in someone who has been taking ketamine/esketamine regularly for weeks or months.

**TCPR: What do we know about esketamine withdrawal?**

**Dr. Williams:** There's a possibility that patients could become more suicidal after the drug is discontinued. We don't know this for sure, but there's a signal in the FDA-registration studies. It wasn't statistically significant, so the drug got approved, but there were 6 deaths in the study, and this occurred after the open-label esketamine phase, so they had all been getting active treatment. Three of them were definite suicides, and these suicides occurred after their last esketamine dose: 4 days, 12 days, and 20 days after (www.fda.gov/media/121376/download). The FDA concluded that the deaths may have been due to the severity of the depression rather than the drug. However, we don't see suicides with that kind of frequency in studies of rTMS or ECT that enroll a similar population. Furthermore, the patients who died by suicide had no signs of suicidality in detailed assessments done during the study, which suggests it may have come on during the withdrawal period.

**TCPR: You're suggesting that a drug-withdrawal effect might be behind those suicides. Do we know anything about the mechanism of action there?**

**Dr. Williams:** Yes. We had a surprising finding last year with IV ketamine that might explain it. Our group showed that ketamine's antidepressant effects are cancelled when you block opioid receptors with the opioid antagonist naltrexone, which means that ketamine probably has direct or indirect opioid properties (see *TCPR*, June/July 2019). Now, does that mean that there's an opioid-like withdrawal when esketamine is stopped? We don't know, but it's possible. Ketamine also has glutamatergic effects on the NMDA receptor, but I don't think that NMDA withdrawal would cause a problem. Otherwise we'd be seeing suicidality after patients stop memantine (Namenda).

**TCPR: Sounds like more research is needed there, but it's concerning.**

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Expert Interview

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**Dr. Williams:** Yes. We just received a grant from the American Suicide Foundation to investigate whether buprenorphine can prevent this problem and extend IV ketamine's antidepressant effects after it is stopped. Like IV ketamine, buprenorphine has positive studies in treatment-resistant depression and in suicidality, but there's no known risk or even a signal of suicide during its withdrawal (see *TCPR*, February 2019).

**TCPR: Does it concern you that we haven't found anything to prevent depressive relapse after a course of ketamine/esketamine?**

**Dr. Williams:** Yes. So far the only thing that works is more ketamine/esketamine, which raises questions about potential tolerance, withdrawal, and addiction. Again, we don't know that those things are happening; we just don't have enough studies to rule them out. Riluzole was tried as a continuation agent, which like ketamine has glutamatergic effects, but it did not work (Mathew SJ et al, *Int J Neuropsychopharmacol* 2010;13(1):71–82). So it will be interesting to see if going through the opioid receptor continues the effects.

**TCPR: Relapse is a problem after ECT as well. What can we do there?**

**Dr. Williams:** ECT has a rich literature on this, and there's good evidence that nortriptyline or venlafaxine can prevent episodes after a course of ECT. Lithium can also work, either alone or as antidepressant augmentation. Another strategy is to start an antidepressant that the patient responded to in the past and use that for prevention (Gill SP et al, *J ECT* 2019;35(1):14–20). Most patients do require maintenance ECT, at least temporarily. Those booster sessions are usually given 1–4 times a month and can be slowly tapered.

**TCPR: What are the relapse rates after rTMS?**

**Dr. Williams:** A typical course of rTMS is 5 treatments a week for 6 weeks. Each treatment takes 30–60 minutes. Afterwards, about two-thirds of patients remain well for up to 6 months without any booster sessions. If we add in booster sessions, the rate of sustained benefits goes up to 85%–90%. So rTMS appears to be more durable than esketamine, which requires booster treatments to keep it working. Also, keep in mind esketamine is an antidepressant augmentation strategy, so the patients remained on an antidepressant after stopping it. In the case of rTMS, some of the patients who stayed well were not taking any antidepressants.

**TCPR: So from a long-term perspective, rTMS seems better. What about in the short term?**

**Dr. Williams:** Ketamine and esketamine's main advantage is that they can work quickly, within hours, which is why it has a role in the ER. rTMS takes 4–6 weeks to work. Otherwise, rTMS and ketamine have comparable remission rates. They haven't been compared head to head, but both have remission rates of 20%–30%. ECT is the one that shines here. A recent meta-analysis estimated the remission rate on ECT at 48%. So ECT wins for efficacy, conventional rTMS wins for safety and tolerability, and esketamine wins for speed. (See "Interventional Therapies for Depression" table below.)

**TCPR: So for now, if patients respond to esketamine or ketamine, they're likely to require continuation treatments. What are ketamine's long-term risks?**

**Dr. Williams:** The biggest one is bladder inflammation or cystitis, which has been seen in people who are addicted to ketamine. It is unclear if this is a risk with therapeutic doses of esketamine or IV ketamine, and it may in fact not be. That was first reported in people who were abusing ketamine in Malaysia, and it's likely they were taking much higher doses than what we use clinically (Lee P et al, *Malays Fam Physician* 2009;4(1):15–18). Since those reports came out, they've clarified the mechanism a bit, and it seems that ketamine abuse can lead to cellular death in the bladder and fibrotic changes in the nerves that innervate the bladder. It's a significant problem; about 50% of ketamine abusers are affected (Jhang JF et al, *Neurourol Urodyn* 2019;38(8):2303–2310).

**Interventional Therapies for Depression**

| | Esketamine | rTMS | ECT |
|---|---|---|---|
| **Advantages** | Rapid antidepressant and antisuicide effects within hours<br>Possibly works in bipolar depression, but ECT and rTMS have better evidence there | Best tolerability of the three<br>Works in bipolar and unipolar depression | Best efficacy of the three<br>Works in bipolar and unipolar depression<br>Particularly useful for psychotic depression and catatonia<br>Neuroprotective |
| **Disadvantages** | Transient dissociation and hypertension<br>Long-term maintenance is required, but long-term risks are not clear; these potentially include bladder inflammation, cognitive problems, addiction, and withdrawal problems<br>May be neuroprotective or neurotoxic | Seizure risk | Memory loss that may persist after treatment<br>Headaches and transient hypertension during treatment<br>Requires anesthesia<br>Patients usually need transportation to sessions and cannot work during treatment |
| **Treatment Schedule** | 8 weeks, starting at 2 times per week and tapering to once weekly after 4 weeks; doses are given intranasally in a monitored setting<br>Maintenance treatment is required 1–2 times per month | 6 weeks at 5 times per week<br>Maintenance sessions are rarely needed | 4 weeks at 3 times per week<br>Monthly maintenance sessions may be needed |

**TCPR: That explains the song about ketamine by Trampolene: "Your mind might be fine, but your bladder is shredded." Is the mind really fine after long-term ketamine use?**

**Dr. Williams:** Not if it's abused. Ketamine has the potential to be neurotoxic or neuroprotective, and it probably depends on the frequency of use. Long-term ketamine abuse has been associated with cognitive problems and loss

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# Antipsychotic Maintenance: How Long Is Enough?

*Chris Aiken, MD. Editor-in-Chief of* The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*

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

*Your 58-year-old patient started risperidone to augment lithium 2 years ago. It got her out of a severe mania, and she has stayed well since then. Now she's worried about long-term risks and wondering if it's time to come off.*

Augmentation with an atypical antipsychotic may offer rapid relief from mania and depression, but antipsychotics' potential side effects are substantial. They include hyperlipidemia, diabetes, obesity, and tardive dyskinesia, the latter increasing at a rate of 2.6% with each year of use. These side effects tend to build gradually over time, so it's important to know when it's clinically appropriate to try stopping the antipsychotic and possibly continuing solo with a mood stabilizer or antidepressant.

Around a dozen industry-supported trials have looked at this question in both bipolar and unipolar disorders. These studies all followed a similar design: They started with patients who recovered with antipsychotic augmentation and then tested what happens when the antipsychotic is withdrawn after 2–3 months of treatment. Typically half the patients continued with the antipsychotic and the other half were switched to placebo. The patients were then followed for a long stretch—from 6 months to 2 years—and the rate of relapse was carefully tracked (Lindström L et al, *J Affect Disord* 2017;213:138–150; Kato M et al, *CNS Drugs* 2013;27 Suppl 1:S11–19).

The consensus of these studies is that continuing the antipsychotic prevents relapse into new mood episodes, but there's a catch. Most of these studies withdrew the antipsychotic within the first few months after recovery, which is a particularly vulnerable time for patients. What if the antipsychotic were stopped later, after 6 months of recovery?

We could find only a single study that looked at this question, and it was in bipolar I disorder. This non-industry-sponsored study enrolled 159 patients who had recovered from bipolar mania after their mood stabilizers were augmented with an antipsychotic, either risperidone or olanzapine. Patients were then randomized into 1 of 3 groups: 1) Continue the antipsychotic for a year; 2) Switch to a placebo after 2–6 weeks of recovery; or 3) Switch to a placebo after 6 months of recovery. All groups were kept on their original mood stabilizer (lithium or valproate). The result: Patients who stopped the antipsychotic after 6 months had the same risk of relapse as those who stayed on the antipsychotic (65%), but the risk was significantly higher when the medication was stopped after 2–6 weeks (87%). Those are high relapse rates across the board, but that's not uncommon in mania (Yatham LN et al, *Mol Psychiatry* 2016;21(8):1050–1056).

That study suggests that antipsychotics can be safely discontinued after 6 months of recovery from mania. In depression, antipsychotics are overall less effective as preventative agents than they are for mania. Among the agents studied, only quetiapine has successfully prevented depression in controlled trials, 2 in bipolar disorder and 1 in unipolar (Liebowitz M et al, *Depress Anxiety* 2010;27:964–976; Lindström L et al, *J Affect Disord* 2017;213:138–150). Those trials tested discontinuation at 3 months. No one has tested whether 6 months of maintenance would be adequate in depression, but we have a hint that it might from the studies of antidepressant discontinuation. In those trials, most of the relapses were due to discontinuation of the antidepressant before 6 months of stabilization, according to a meta-analysis of 45 controlled trials (Baldessarini RJ et al, *J Clin Psychopharmacol* 2015;35(1):75–76).

In practice, I usually wait 6 months before trying antipsychotic discontinuation. The decision is collaborative and different for each patient. If we decide to come off, I'll taper slowly, lowering the dose every 2 weeks. I'll encourage the patient to build habits known to prevent mood episodes, such as mindfulness, exercise, the Mediterranean diet, and regular sleep and wake times. If the taper does not work, I may try again after 1–2 years. About half the time, the second attempt is a success.

**TCPR VERDICT:** In mood disorders, wait at least 6 months after recovery before attempting to discontinue an adjunctive antipsychotic. Taper slowly, watch for relapse, and encourage lifestyle changes to prevent new episodes.

***To learn more, listen to our 1/27/20 podcast, "Industry Bias in Antipsychotic Trials: An Interview with Nassir Ghaemi."*** Search for "Carlat" on your podcast store.

## Expert Interview

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of brain tissue in the frontal lobes and left temporoparietal regions (Liao Y et al, *Brain* 2010;133(7):2115–2122). The effect is likely due to ketamine because it is dose dependent, and it's been replicated in animal studies with careful controls. On the neuroprotective side, ketamine does increase brain-derived neurotrophic factor (BDNF). It may be that a bit of ketamine is fine and a lot is not. There have been no reports of neurotoxicity with clinical use of ketamine and esketamine, although we haven't really been looking for that.

**TCPR: You've pointed out a lot of gaps in our knowledge about esketamine. What type of research needs to be done?**

**Dr. Williams:** I would love to see a head-to-head trial of esketamine and conventional rTMS. If esketamine were to beat conventional rTMS in long-term safety and efficacy, that would likely change minds about its use.

**TCPR: Thank you for your time, Dr. Williams.**

***To learn more, listen to our 1/13/20 podcast, "Getting Uncomfortable With Esketamine".*** Search for "Carlat" on your podcast store.

# Research Updates IN PSYCHIATRY

## DEPRESSION

### *TMS: Deeper Is Not Better*

**REVIEW OF: Filipcic I et al, *J Psychiatr Res* 2019;114:113–119**

**TYPE OF STUDY: Randomized single-blind controlled trial**

Seven transcranial magnetic stimulation (TMS) devices are FDA approved for depression, but only one—the Brainsway—is distinctly different from the others. Brainsway uses a patented H1 coil that penetrates deeper into the cortex than the standard figure-8 coil. Brainsway's marketing materials suggest that deeper is better, but the two versions of TMS have never been compared head to head—until now.

In this non-industry-sponsored study, 228 patients with moderate major depression were randomized to 1 of 3 arms over 4 weeks: TMS with the H1 coil, TMS with the figure-8 coil, or 2 visits of standard psychopharmacology. All patients were taking an antidepressant and stayed on that medication during the trial. The evaluators were blinded, but the patients knew which treatment they were getting. The primary outcome was remission on the 17-item Hamilton Rating Scale for Depression (HAMD-17). The study was funded by a public psychiatric hospital in Croatia, which is where the treatments were conducted.

The H1 coil and figure-8 coil were not statistically different on the primary outcome of remission, although both were superior to the standard psychopharmacology group. On secondary measures, the H1 coil had a greater response rate on the HAMD-17 than the figure-8 coil, but there were no differences in the total change on the HAMD-17 on quality-of-life measures. Likewise, safety and tolerability were equal for both devices.

These mixed results are similar to a recent meta-analysis that looked at outcomes in 19 studies of the 2 coils. The H1 coil led to greater reductions in depression severity, but the figure-8 coil had a slight advantage in remission rates (Gellersen HM and Kedzoir KK, *BMC Psych* 2019;19(1):139).

#### TCPR'S TAKE

Both types of TMS work, and deeper stimulation with the H1 coil does not work any better than earlier figure-8 coils.

*—Edmund S. Higgins, MD.* Dr. Higgins has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

## CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. As a subscriber to *TCPR,* you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

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*Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives (LO) are listed on page 1.*

1. The estimated risk of tardive dyskinesia in an adult under age 65 who has been taking an atypical antipsychotic for 10 years is ____. (LO #2)
   [ ] a. 5% [ ] b. 20% [ ] c. 40% [ ] d. Over 55%

2. According to Dr. Williams, there is no association between long-term ketamine abuse and subsequent cognitive issues. (LO #1)
   [ ] a. True [ ] b. False

3. In general, antipsychotics are less effective as preventative agents for depression than they are for mania in patients with bipolar disorder. According to recent studies, only ____ has successfully prevented depression in controlled trials. (LO #3)
   [ ] a. Lurasidone [ ] b. Olanzapine [ ] c. Quetiapine [ ] d. Ziprasidone

4. According to a 2019 study, TMS with the H1 coil was not superior to TMS with the figure-8 coil for remission from depression. (LO #4)
   [ ] a. True [ ] b. False

5. Which side effect occurs in almost 50% of people with long-term ketamine abuse? (LO #1)
   [ ] a. Hearing loss or tinnitus [ ] c. Bladder inflammation or cystitis
   [ ] b. Visual hallucinations [ ] d. Neuropathy

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## In Brief: Antipsychotic Update

**FDA Clears the Path for Magic Mushrooms.** Psilocybin, the psychedelic compound in magic mushrooms, was fast-tracked by the FDA for major depression in November 2019. A phase 2 trial is currently underway by the nonprofit Usona Institute with completion expected by 2021. A separate company, Compass Pharmaceuticals, is testing psilocybin in treatment-resistant depression.

What we know about this serotonin-2 agonist is that it brought rapid relief to treatment-resistant depression in a small open-label trial in 2016. Improvement was seen after 2 doses, and the gains were maintained 6 months later without further dosing. Confirmation of these antidepressant effects has been limited to a small randomized, placebo-controlled trial in patients with depression and terminal cancer.

Psilocybin's antidepressant effects appear linked to the quality of the spiritual experiences induced by the drug. When it works, it enhances gratitude, forgiveness, death transcendence, religious faith, and closeness to nature and humanity. On the other hand, psilocybin can cause frightening alterations of consciousness. The drug is usually administered in the context of a supportive psychotherapy to foster a safe environment and bring out the positive in its transcendent effects. Similar spiritual experiences have been described on ketamine, and we covered those reports in our July 8, 2019 podcast, "The Secret History of Ketamine."

***To learn more, listen to our 2/3/20 podcast, "Psilocybin, Ketamine, and the Spiritual Brain."*** Search for "Carlat" on your podcast store.