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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Overdiagnosis

Learning Objectives

After reading these articles, you should be able to:

1. Evaluate the efficacy of atomoxetine as a treatment for ADHD and other psychiatric disorders.
2. Identify psychiatric disorders that are commonly over- and underdiagnosed in practice.
3. Summarize some of the current research findings on psychiatric treatment.

Atomoxetine: Myths and Truths

C. Jason Mallo, DO. Attending psychiatrist, Maine Medical Center, Portland, ME.

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

Highlights From This Issue

Adult ADHD, PTSD, bipolar II, major depression, and borderline personality disorder are overdiagnosed in psychiatry, while schizophrenia is underdiagnosed, according to Dr. Joel Paris.

Atomoxetine (Strattera) and viloxazine (Qelbree) are not as effective as stimulants for ADHD, and their antidepressant-like mechanism poses risks for patients with bipolar disorder.

We may be dosing lurasidone (Latuda) too low in schizophrenia.

Atomoxetine (Strattera) is approved for ADHD in children and adults but has also been explored in many other disorders. That has led to some myths and truths that we'll explore here.

First, a little about atomoxetine's mechanism of action. Atomoxetine is a selective norepinephrine reuptake inhibitor, a mechanism shared by maprotiline, a long-forgotten tricyclic; reboxetine, an antidepressant used in Europe; and viloxazine, the new nonstimulant on the block branded as Qelbree. By blocking presynaptic norepinephrine reuptake, atomoxetine increases synaptic norepinephrine and dopamine in the frontal lobes. Because it does not affect dopamine in the striatum, you don't have to worry about abuse. Therefore, atomoxetine is ideal for ADHD comorbid with substance use disorders.

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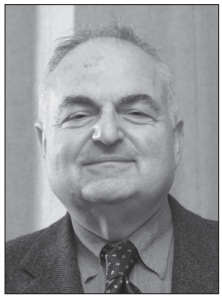
Q&A With the Expert

Overdiagnosis in Psychiatry
Joel Paris, MD

Professor emeritus at McGill University, and senior psychiatrist and research associate at Sir Mortimer B. Davis-Jewish General Hospital. Dr. Paris is the former editor of the Canadian Journal of Psychiatry *and the author of 25 books including* Overdiagnosis in Psychiatry, *2nd ed. (Oxford University Press; 2020).*

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



TCPR: Which disorders are the most overdiagnosed in psychiatry?

Dr. Paris: At the top of the list are major depression, PTSD, bipolar II, adult ADHD, and—this one is a recent addition because it used to be underdiagnosed—borderline personality disorder. Each of these conditions may be underdiagnosed in some settings as well, but they have also been pushed toward diagnostic expansion.

TCPR: That sounds like a lot of my patients. What are we doing wrong?

Dr. Paris: Part of the problem is not using the DSM criteria. Many clinicians are rushed, and the criteria are difficult to memorize. Nearly half of patients whose primary care provider diagnosed them with depression don't actually meet the DSM criteria for it (Mojtabai R, *Psychother Psychosom*

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Atomoxetine: Myths and Truths
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Myth: Atomoxetine is useful for depression

Atomoxetine was originally developed as an antidepressant, but although open-label trials were promising, that promise fell flat in more rigorous trials (Corp SA et al, *J Clin Psychiatry* 2014;75(9):1010–1018; Weintraub D et al, *Neurology* 2010;75(5):448–455). To target ADHD and depression, you're better off prescribing an antidepressant with benefits in ADHD, such as bupropion or desipramine.

Truth: Atomoxetine is useful for ADHD

Atomoxetine was released in 2002 as the first nonstimulant for ADHD and became generic in 2017. Multiple controlled studies support its use. With its NNT* of 5–7, it appears just as effective as other nonstimulants, including viloxazine, the latest antidepressant-like medication repurposed for ADHD (Nasser A et al, *Int J Clin Pract* 2021;75(8):e14330). Atomoxetine has not been compared directly with nonstimulants, but stimulants (NNT = 2–4) have been found more effective than atomoxetine in head-to-head trials. Still, atomoxetine has some advantages. For instance, it can be given once daily and has sustained benefit throughout the day, without rebound effects. Because it's unscheduled, you can prescribe refills. Plus, in our experience, some patients respond preferentially to atomoxetine. A disadvantage is that while symptoms can improve within a couple of weeks on atomoxetine, full benefit can take up to 10 weeks to manifest.

*NNT is the number of patients needed to treat to achieve a meaningful response beyond the placebo effect. Lower numbers are better.

Myth: Atomoxetine is better tolerated than stimulants

There's a myth that atomoxetine, like stimulants, increases energy. However, comparison trials show atomoxetine is more associated with somnolence, while stimulants are more associated with insomnia. Atomoxetine causes fatigue at a rate of one in 20 patients, and that fatigue can be intense. In post-marketing surveillance reports to the FDA, atomoxetine ranked second among 30 medications with antidepressant structures for causing fatigue that was severe enough to prompt a report to the FDA.

Both atomoxetine and stimulants increase heart rate and blood pressure, and the FDA recommends that you periodically check these vital signs. Atomoxetine is contraindicated in poorly controlled cardiovascular disease. It may prolong the QTc, but there are few reports of this, and ordering a baseline ECG is not necessary.

Truth: Atomoxetine has other risks

Other disorders that warrant caution with atomoxetine include glaucoma, tics, seizures, and hepatic disease. Like antidepressants, atomoxetine has a warning about suicidal ideation in children and adolescents. This risk has shown up in case reports but has not been common enough to reach statistical significance in controlled trials (Bangs ME et al, *J Child Adolesc Psychopharmacol* 2014;24(8):426–434). Its safety in pregnancy and lactation is unknown.

Myth: Atomoxetine is a good choice to augment stimulants

The safety of this combination is not fully established, though some reports support it. To avoid cardiovascular events, supplementing stimulants with alpha-agonists may be a better option. The alpha-agonist guanfacine has controlled trial evidence to augment stimulants, and although guanfacine's effects were meager, they at least reached statistical significance and reduced some stimulant side effects like insomnia and hypertension (McCracken JT et al, *J Am Acad Child Adolesc Psychiatry* 2016;55(8):657–666).

Truth: Drug interactions matter with atomoxetine

Atomoxetine is metabolized through a single hepatic pathway—CYP2D6. That means it can reach high levels if this pathway is blocked by strong 2D6 inhibitors like fluoxetine, paroxetine, duloxetine, high-dose sertraline (≥ 150 mg/day), or bupropion. Levels can also surge in patients who are poor metabolizers at 2D6, with peak levels fivefold higher in this population, and poor metabolizers are twice as likely to stop the drug due to side effects. If your patient is taking a strong 2D6 inhibitor or is a known poor metabolizer at 2D6, start with the lowest possible dose, raise it half as fast, and aim for a target dose that's 50%–75% less than usual. As to whether you should run a genetic test before starting atomoxetine, the FDA has left the choice up to clinicians. They recommend lower doses for known 2D6 poor metabolizers, but they don't recommend routinely testing this enzyme.

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Atomoxetine: Myths and Truths
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Myth: Atomoxetine is safe in bipolar disorder

The noradrenergic antidepressants generally have the highest risk of inducing mania, particularly venlafaxine and the tricyclics (Melhuish Beaupre LM et al, *J Clin Psychopharmacol* 2020;40(2):180–185). Atomoxetine's risk in this regard is unknown, but its noradrenergic mechanism makes it suspect, and there are case reports of mania and psychosis on it (Reed VA et al, *CNS Drugs* 2016;30(7):603–628). If mania and psychosis are a concern, stick with the alpha-agonists guanfacine and clonidine, which have small studies supporting their safety and possible benefits in bipolar disorder and schizophrenia (Kontaxakis V et al, *Acta Psychiatr Scand* 1989;79(1):108–110; Arnsten AFT and Jin LE, *Yale J Biol Med* 2012;85(1):45–58).

Truth: Atomoxetine may have other uses

For ADHD and anxiety, atomoxetine may have a role. In a 14-week randomized controlled trial of 442 adults with ADHD and social anxiety disorder, atomoxetine outperformed placebo on markers of ADHD ($p < 0.001$) and social anxiety ($p < 0.001$). However, the results may have been influenced by the interaction of each condition on the other, and the industry-sponsored study has not been independently validated (Adler LA et al, *Depress Anxiety* 2009;26(3):212–221).

Atomoxetine may also be useful for binge eating and obesity, at least according to two small randomized controlled trials. In a 10-week study of 40 adults with binge eating disorder, atomoxetine reduced binge frequency ($p = 0.034$) and weight ($p = 0.018$) (McElroy SL et al, *J Clin Psychiatry* 2007;68(3):390–398). It also reduced weight ($p < 0.0001$) in a 12-week study of 20 adults with obesity (Gadde KM et al, *Int J Obes (Lond)* 2006;30(7):1138–1142). Note that these studies had industry funding as well.

How to Use Atomoxetine for Adults
Start 40 mg/day and increase after 1–4 weeks to 80 mg/day. If you don't get an adequate response in two months, you can increase the dose to a max of 100 mg/day.
Administer a single daily dose in the morning or two evenly divided doses.
Don't worry about food when dosing, as food does not affect absorption.
Reduce the dose by 50%–75% in patients who are poor metabolizers at CYP2D6 or who are taking a strong 2D6 inhibitor.
For reducing side effects, split the dose. Take with food for nausea and at night for sedation.
Monitor heart rate and blood pressure.

TCPR VERDICT: Atomoxetine's career may be marked by unfulfilled hopes, but it still has a role. Consider it for ADHD when first-line options are ineffective, a controlled substance is undesirable, or the patient has comorbid social anxiety or binge eating disorder.

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Expert Interview
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2013;82(3):161–169). But even if the criteria are used, the DSM still has a pretty low bar for major depression. In reality, depression is a universal phenomenon that is on a continuum, and you make a slice somewhere. But where you make that slice is not really evidence based.

TCPR: When you say "a low bar for depression," what do you mean?

Dr. Paris: The two-week cutoff was a big mistake. Lots of people have depression that self-resolves after a few weeks. If the DSM had said six or seven weeks, I think we'd be in less trouble. Another problem is that the DSM lumps both mild and severe cases under the diagnostic umbrella of "major depressive disorder." That was not the case before 1980 with DSM-III, and there are reasons to separate mild and severe cases. We know, for example, that antidepressants don't separate very well from placebo in mild cases—their efficacy is only undisputed in severe depression (Fournier JC et al, *JAMA* 2010;303(1):47–53). Treating everyone who meets criteria for major depression with an antidepressant is simply not evidence based. The UK has stepped away from this with the NICE guidelines, which do not recommend antidepressants for mild depression. But the APA and Canadian guidelines still allow it.

TCPR: Do clinicians in the UK use psychotherapy for mild depression?

Dr. Paris: Yes, and patients there have better access to it because the British hired psychologists to bring cognitive behavioral therapy (CBT) for anxiety and depression into the National Health Service.

PTSD, Bipolar Disorder, and ADHD

TCPR: How is PTSD overdiagnosed?

Dr. Paris: PTSD has a big problem with criterion A, which requires the presence of a trauma. Originally the patient had to experience or witness the trauma, but now just hearing about a traumatic event is enough to meet the criterion. And PTSD is a diagnosis beloved not only by clinicians, but by patients too. They actually want to have PTSD because it means somebody else is at fault, not them, and they're a victim.

TCPR: How is bipolar disorder overdiagnosed?

Dr. Paris: The problem is not with standard bipolar I. That kind of mania is unmistakable. But

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Expert Interview

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bipolar II only came in with DSM-IV, and the criteria are kind of fuzzy. I think clinicians reach for their prescription pad when they see mood swings of any kind because they think they're seeing a case of bipolar II. Mark Zimmerman showed that patients who screen positive for bipolar disorder on the Mood Disorder Questionnaire are just as likely to have borderline personality disorder as they are to have bipolar on closer examination (Zimmerman M et al, *J Pers Disord* 2019;33(4):533–543). Mood swings are a key feature of borderline personality disorder, and that can confuse the picture for many clinicians.

TCPR: And ADHD?

Dr. Paris: That diagnosis has gone up dramatically in the last 20 years in adults and children. Ten times as many people are taking stimulant drugs compared to a couple of decades ago. Nearly one in five adolescent boys are diagnosed with ADHD (Visser SN et al, *J Am Acad Child Adolesc Psychiatry* 2014;53(1):34–46). Adult ADHD used to be rare, but in the National Comorbidity Survey the rate was one in 23, and that was while using the childhood-onset requirement, which is often ignored in practice (Kessler RC et al, *Am J Psychiatry* 2006;163(4):716–723). Previously, symptoms had to start before age 7 to make a diagnosis, and then DSM-5 extended that to age 12.

TCPR: We are seeing adults present with symptoms of ADHD but no evidence of the disorder in childhood. What could be causing that?

Dr. Paris: Patients with "adult ADHD" have a lot of psychiatric comorbidities that could explain their cognitive problems. Problems with attention and executive functioning are well documented in mood, anxiety, personality, sleep, and substance use disorders (Paris J. *Overdiagnosis in Psychiatry.* New York, NY: Oxford University Press; 2020). Terrie Moffitt's group followed a New Zealand birth cohort for 40 years and found that most people who had symptoms of ADHD in adulthood did not have those symptoms as children (Agnew-Blais JC et al, *JAMA Psychiatry* 2016;73(7):713–720). This suggests that the symptoms do not have the same etiology as true ADHD.

"Patients with 'adult ADHD' have a lot of psychiatric comorbidities that could explain their cognitive problems. Problems with attention and executive functioning are well documented in mood, anxiety, personality, sleep, and substance use disorders."

Joel Paris, MD

TCPR: The problem with age of onset in that study does cast doubt on the concept of adult ADHD. But the study ended up having a different effect. It generated a lot of headlines announcing the discovery of a new diagnosis: adult-onset ADHD.

Dr. Paris: Well, Dr. Moffitt did open the door for this in her article, but I would say, "Why call it ADHD?" In the Moffitt study, most of the patients with "adult-onset ADHD" had a history of mood, conduct, or substance use disorders that might have explained their adult ADHD symptoms. Another problem with ADHD is the inclusion of the inattentive subtype, which took place with DSM-IV in 1994.

TCPR: What is the problem with inattentive ADHD?

Dr. Paris: It opened the door to overdiagnosis. Now almost anybody who is troubled can come up with a story about their inattention, and they do. Hyperactivity is more observable, so it's harder to overdiagnose, and our research is most robust with the hyperactive types. We know what these patients are at risk for later on—things like substance use and antisocial behavior.

Underdiagnosis in Schizophrenia

TCPR: If some disorders are overdiagnosed, are others underdiagnosed?

Dr. Paris: Schizophrenia is probably underdiagnosed. I think the problem there is not with the definition (although the overlap with bipolarity is still pretty controversial), but with its difficult prognosis. I think clinicians would rather call it schizoaffective disorder, which has a better prognosis because it lacks the negative symptoms, or just nonspecific psychosis. However, there has been a movement to recognize early signs of schizophrenia, and that is changing things.

TCPR: How so?

Dr. Paris: The idea is that if you recognize prodromal signs and intervene early, you may be able to obviate that bad prognosis. Early intervention proponents haven't proven their case completely at all, but they have helped shift the perspective. Interestingly, the evidence is stronger for CBT than it is for antipsychotics when it comes to preventing schizophrenia in youth at risk (Nelson B and McGorry P, *Child Adolesc Psychiatr Clin N Am* 2020;29(1):57–69).

Borderline Personality Disorder

TCPR: What is lost by missing a personality disorder?

Dr. Paris: Outcomes are not as good. Whether it's pharmacotherapy, psychotherapy, or even electroconvulsive therapy, a lot of research shows that people with personality disorders do not do as well when given standard treatments for other disorders. These patients require more specialized methods.

TCPR: Which personality disorders are most important to recognize in practice?

Dr. Paris: Borderline and antisocial. Those are the only ones that have serious research behind them. We have a good etiological theory for borderline personality disorder. Emotional dysregulation is a heritable trait that is then amplified by an invalidating environment. There's more to the theory, but that explanation captures its essence, and it was one

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of Marsha Linehan's greatest contributions.

TCPR: What is an invalidating environment?

Dr. Paris: It refers to growing up in a situation where your family isn't interested in your emotions. "Emotional dysregulation" means a patient is unusually sensitive—they have "thin skin" and high neuroticism, where everything bothers them and they can't calm down. And that is a highly heritable trait. If they grow up in an environment where somebody around them says, "I understand how you feel. You have every right to feel that way. Let's figure out how you can get past this. You know how to calm yourself and think of a way to solve the problem," then it doesn't turn out so bad. But what patients with borderline personality disorder describe to me is, "Nobody was interested in my feelings. I was told to buck up, get over it, and not make a big deal out of it."

TCPR: So it's not necessarily trauma that causes it.

Dr. Paris: Correct. One of the great myths about borderline personality disorder is that it's due to trauma. While trauma is common in borderline personality disorder, fewer than half the cases actually have a significant history of trauma. Often, when you take a closer look at a patient's history, you'll find they had evidence of a personality disorder before the trauma, and borderline personality disorder affects judgment, impulsivity, and relationships in ways that can put people at risk for trauma (Paris J. *Treatment of Borderline Personality Disorder*. 2nd ed. New York, NY: Guilford Press; 2020).

TCPR: Some have suggested that cyclothymia is the underlying temperament behind borderline personality disorder.

Dr. Paris: I think emotional dysregulation is a more accurate term. Cyclothymic disorder involves frequent mood cycles—hypomania, depression, mixed states. But moods last longer than emotional dysregulation. Patients will describe it like this: "I get upset and I blow sky high. It takes me hours to calm down." And this is nothing like hypomania, which is a consistent state of high energy and irritable or elevated mood for four days or more. With emotional dysregulation, the symptoms usually come on as a direct reaction to an interpersonal stress. This persists for a few hours and then the patient sleeps it off, and the next day something else happens.

TCPR: You mentioned that borderline personality disorder used to be underdiagnosed, but now that's changing.

Dr. Paris: Yes, and this gets back to prognosis. People used to think borderline personality disorder was incurable, but now that we have effective treatments for it like DBT and other psychotherapies, I'm having to tell patients, "No, you actually don't have borderline personality disorder" and they're disappointed.

TCPR: How would you explain to a patient that they don't have a psychiatric disorder or that their problems are not severe enough to warrant medication?

Dr. Paris: Some people might be relieved to hear that, while others might be outraged. I think it depends on how they see themselves. One of my colleagues at McLean Hospital described something she called "emotional hypochondriasis" where people feel that their psychology is sick and they hold onto that as a kind of identity. So this is a complicated question. I tell residents, "Some people are going to walk out of here mad, and you'll have to get used to it." But I don't have a simple answer.

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

To learn more, listen to our 9/6/21 podcast, "Overdiagnosis."
Search for "Carlat" on your podcast store.

Research Updates IN PSYCHIATRY

DEPRESSION

Psilocybin vs Escitalopram for Depression

REVIEW OF: Carhart-Harris R et al, *New Engl J Med* 2021;384(15):1402–1411

STUDY TYPE: Randomized controlled trial

Psilocybin is, among other things, a serotonin 2A agonist responsible for the psychedelic properties of magic mushrooms. Back in 1960, Sandoz (now Novartis) began marketing psilocybin to enhance the effects of psychotherapy, but production was stopped soon after due to concerns about its abuse liability and potential to induce psychosis. Now, over a half-century later, the FDA has granted psilocybin breakthrough status and fast-tracked research to explore its potential antidepressant effects. Those effects have been associated with psilocybin's ability to induce transcendent spiritual states. Similar to how it was used in the 1960s, modern-day psilocybin is delivered along with supportive psychotherapy to enhance those beneficial effects while maintaining close oversight in case patients experience a "bad trip."

In this double-blind study, investigators randomized 59 patients with moderate to severe depression to receive either psilocybin 25 mg (given twice: on day 1 and on day 21) or escitalopram 10–20 mg/day over the course of six weeks. Importantly, most patients included in the trial were not treatment resistant, having taken on average only two psychotropic medications in the past. Although there was no placebo group, the escitalopram group received a microdose of psilocybin so all patients

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could be informed that they were receiving it—a clever maneuver that aimed to standardize expectations.

The primary outcome of interest was reduction in scores on the 16-item Quick Inventory of Depression Symptomatology-Self Report (QIDS). Both groups improved, with overall scores favoring psilocybin over escitalopram: 8- versus 6-point reduction in depression scores on the QIDS and response rates of 70% versus 48%. However, these differences were not statistically significant.

On questioning, patients receiving psilocybin reported greater perceived improvements "in the ability to cry and feel compassion, intense emotions, and pleasure." Adverse effects were similar between the two groups, and there were no reports of perceptual changes, psychosis, or other serious problems with psilocybin.

TCPR'S TAKE

The study ostensibly shows that psilocybin is as effective as escitalopram for depression. However, the research suffers from two major flaws. First, the researchers failed to assess the integrity of the blind. Given that patients were mostly self-referred and highly motivated, and that 72% had used psilocybin in the past, they could very possibly have guessed whether they were receiving a therapeutic dose of psilocybin. Second, lacking a placebo group, we can't know whether psilocybin even worked. Nearly 50% of SSRI trials fail to separate from placebo, and that's with sample sizes 10 times larger than the ones used in this study. It's possible that neither psilocybin nor escitalopram were effective.

The *New England Journal of Medicine* rarely publishes psychiatric research, and with the level of interest surrounding psilocybin, you will no doubt hear more about this pilot study. Unfortunately, the study fails to move the needle much, and it would be premature to recommend psilocybin to your patients until larger, placebo-controlled studies are conducted.

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

DEPRESSION

Pilot Study of Ketamine vs ECT for Major Depression

REVIEW OF: Kheirabadi D et al, *J Clin Psychopharm* 2020;40(6):588–593

STUDY TYPE: Randomized controlled trial

Electroconvulsive therapy (ECT) has long been the gold standard for severe or treatment-refractory depression (TRD). However, it has two major drawbacks: it involves anesthesia and it may be associated with memory impairment. Ketamine has emerged as a possible alternative to ECT both for TRD and for acute suicidal ideation. Given ketamine's advantage of working quickly, it is of great interest to know how these two very different treatments compare with each other.

In this study, investigators recruited 39 patients with severe depression, TRD, or acute suicidal ideation who were referred for ECT. These patients were then randomized to receive either ECT (n = 12), oral R-ketamine (n = 12), or IM ketamine (n = 15). All three treatments were offered for 6–9 sessions.

Depression scores improved over the course of three weeks in all three groups by about 40%–50% on the Hamilton Depression Rating Scale without significant differences between the groups. Several other differences did emerge, however: 1) Scores on suicidality ratings dropped significantly faster in patients receiving both versions of ketamine—as early as day 1—and remained lower through week 2; 2) The benefits of ECT and ketamine were apparent even one month post-treatment, though ECT appeared to display gains that were enduring yet not statistically significant; 3) Overall, patients receiving ketamine reported significantly higher levels of satisfaction, while patients receiving ECT were more likely to report significantly more cognitive complaints (58% of patients) one month post-treatment.

Ketamine is available in three forms: S-ketamine, R-ketamine, and ketamine (a 50/50 mixture of the two isomers). This study, which took place in Iran, used oral R-ketamine. In the US, intranasal S-ketamine (esketamine) is FDA approved for depression treatment as Spravato. The R- and S-isomers are not interchangable, and there is some evidence that the R-isomer may be even more effective than S-ketamine. The other ketamine arm in this study is identical to the racemic mixture of R- and S-ketamine that is used off-label for depression, except that it was delivered IM, whereas IV is the typical route in the US. Thus, we can't be sure that these results would be the same for the kinds of ketamine used in the US.

TCPR'S TAKE

Given their small sample sizes, pilot studies should always be taken with a grain of salt. Nevertheless, these results are in line with prior research. Ketamine works more quickly than ECT especially for suicidal ideation and appears to be better tolerated, though ECT's benefits may be more enduring. Larger studies will clarify ketamine's optimal dosing, delivery route, and long-term safety, and for now ketamine remains on track to be the best alternative to ECT for severe depression, with a unique role in acutely suicidal patients.

—Michael Posternak, MD.

To learn more, listen to our 9/27/21 podcast, "The Spiritual Origins of Ketamine." Search for "Carlat" on your podcast store.

GENETIC TESTING

Genetic Testing in Depression

REVIEW OF: Perlis RH et al, *Depress Anxiety* 2020;37(9):834–841

STUDY TYPE: Randomized controlled trial

By tailoring medications to a patient's genetic profile, pharmacogenomics promises less medication trial and error, fewer side effects, and better overall outcomes. But does knowing a patient's pharmacogenetic profile really improve treatment for some of the most common illnesses that we see, like depression?

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CME Post-Test

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For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. How does the efficacy of atomoxetine compare to that of other medications in ADHD (LO #1)?
   - [ ] a. Its efficacy is equal to stimulants
   - [ ] b. Its efficacy is equal to other nonstimulant medications
   - [ ] c. It is more efficacious than stimulants
   - [ ] d. It is less efficacious than other nonstimulant medications

2. According to Dr. Paris, which type of patient is most likely to generate false-positive screens on the Mood Disorder Questionnaire? (LO #2)
   - [ ] a. Posttraumatic stress disorder
   - [ ] b. Substance use disorder
   - [ ] c. Attention deficit hyperactivity disorder
   - [ ] d. Borderline personality disorder

3. In a 2020 study involving patients with either severe depression, treatment-refractory depression, or acute suicidal ideation, how did the two ketamine treatment arms compare to electroconvulsive therapy (ECT) (LO #3)?
   - [ ] a. Ketamine produced more cognitive complaints
   - [ ] b. Ketamine reduced suicidal ideation scores significantly faster than ECT
   - [ ] c. Ketamine appeared to display more enduring gains than ECT
   - [ ] d. ECT significantly improved depression compared to ketamine

4. Compared to atomoxetine, an alpha-agonist such as guanfacine or clonidine is less likely to worsen mood in patients with bipolar disorder. (LO #1)
   - [ ] a. True
   - [ ] b. False

5. Which treatment has the strongest evidence for preventing schizophrenia in at-risk youth? (LO #2)
   - [ ] a. Mood stabilizers
   - [ ] b. Cognitive behavioral therapy
   - [ ] c. Antipsychotics
   - [ ] d. Psychodynamic therapy

Research Updates

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So far the controlled trials have been largely negative, but they've mainly focused on the Genesight panel. This trial tested the Genecept panel, which includes most of the genes in the Genesight panel but adds a few pharmacodynamic elements that have only preliminary evidence for use (eg, BDNF, melanocortin, and major histocompatibility complex).

This randomized controlled trial enrolled 314 adults with moderate to severe major depressive disorder who had already failed 1–3 antidepressant medications in the current depressive episode. Half the patients received treatment that was actively guided by the test, while the other half received treatment as usual. The primary outcome, change in Hamilton Depression Rating Scale score, was measured over eight weeks of treatment. The patients and researchers performing the rating scales were blinded to the treatment arm assignment, but the treating provider was not blinded.

At the end of the trial, the changes in depression scores ($p = 0.53$), rates of response ($p = 0.17$), and rates of remission ($p = 0.23$) were all no different between the two groups. Most of the secondary outcomes also showed no difference between the groups, including a self-report rating scale, the Clinical Global Impression-Improvement scale, and patient rating of side effects.

The authors did find that patients were more likely to remit when their medications were concordant with their test results. This finding, however, was only positive on post-hoc analysis, which means it is prone to false positives and should be interpreted with caution.

TCPR'S TAKE

Genecept joins the list of companies that have failed to show any benefit associated with genetic testing, even in patients who did not respond to one or more antidepressants. While this does not support the routine use of genetic testing, it doesn't mean the tests do nothing. Consistent with earlier studies, patients fared worse when their medications were misaligned with their genetic results, but those misalignments are likely too rare to make a measurable difference.

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

To learn more, listen to our 10/4/21 podcast, "A Genetic Test That Didn't Fail." Search for "Carlat" on your podcast store.

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In Brief: Desert Island Diagnoses

In 1974, Drs. Donald Goodwin and Samuel Guze put forth a radical idea. They wanted to pare down the unwieldy list of psychiatric diagnoses to only the most valid:

1. MDD
2. Bipolar disorder
3. Schizophrenia
4. Panic disorder and specific phobias
5. PTSD (provisional)
6. OCD
7. Anorexia and bulimia
8. Somatization and conversion disorder
9. Antisocial personality disorder
10. Borderline personality disorder (provisional)
11. Alcohol & substance use disorders
12. Dementia and delirium

That list was published in their 1974 classic *Psychiatric Diagnosis*. The book is now in its seventh edition, but five decades of research have only elevated two diagnoses to the list: PTSD and borderline personality disorder (reluctant additions, as the editors believed their features overlapped too much with those of other disorders).

The editors of the DSM-III were inspired by this stoicism, but by the time of its release in 1980, the book had grown to include 265 disorders. The DSM editors got around this by adding a warning to many diagnoses, advising that we should not diagnose them if they are better explained by a more strongly validated disorder like one on Goodwin and Guze's list. This warning is easy to miss, but it's one of the most important parts of the book. Without it, the DSM is just a symptom checklist—one that inevitably leads to the kind of diagnostic creep Dr. Joel Paris warns about in this issue.

—Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report