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:
Psychiatric Education

Learning Objectives

After reading these articles, you should be able to:

1. Extrapolate the evidence for optimal use of vilazodone for best patient outcomes.
2. Demonstrate an understanding of current controversies in psychiatry.
3. Summarize some of the current research findings on psychiatric treatment.

Viibryd Goes Generic, But Is It Worth Prescribing?

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

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

After 11 years of market exclusivity, vilazodone (Viibryd) lost its patent in June of 2022. The price of this "multimodal" antidepressant has fallen to $40 a month and may fall further as more manufacturers enter the market. More patients can afford to take it, but whether we should prescribe more vilazodone is less clear.

Multimodal action

Vilazodone wraps the pharmacodynamic effects of the popular SSRI-buspirone combo into one drug. Like an SSRI, it is a potent serotonin reuptake inhibitor, and like buspirone, it is a 5-HT1A serotonin agonist. Vilazodone's manufacturer hoped this dual mechanism would lead to faster onset, more anxiolytic effects, and fewer sexual side effects. At first, those hopes seemed to pan out, but today they only hold up if the data are cherry-picked.

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Highlights From This Issue

Feature article. Vilazodone is now generic, but questions remain about its long-term efficacy, anxiolytic qualities, and effects on sexual function.

Q&A. Dr. Daniel Carlat looks back on 20 years of the *Report*. He comes up skeptical of genetic testing and gives new takes on psychedelics, ketamine, adult ADHD, TMS, and generic drugs.

Research updates. Use caution when switching antipsychotics to aripiprazole in schizophrenia. A new study finds a high rate of acute psychotic exacerbation.

Q&A With the Expert

20 Years of *The Carlat Report*
Daniel Carlat, MD

Medical Director of Inpatient Psychiatry/Chairman of Psychiatry at MelroseWakefield Healthcare. Publisher, Carlat Publishing.

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

TCPR: What led you to start *The Carlat Report* 20 years ago?
Dr. Carlat: I was always interested in writing. When I was 8, I would write poems for Thanksgiving dinners with family in Los Angeles. I kept a daily journal, and still do. In residency, I got interested in psychiatric interviewing and decided to write a short book on the subject, *The Psychiatric Interview.* I sent it out to publishers on a whim, and to my surprise they wanted to publish it. The book became a bestseller and started me down a path that would eventually lead to this publication.

TCPR: What happened next?
Dr. Carlat: Fast forward to October of 2001. I was in private practice in Massachusetts, and a drug rep from Wyeth walked in with a big smile. He was giving my book to other doctors as a freebie and asked if I'd like to give

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Expert Interview
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promotional talks for his company, which made Effexor. "Why not?" I thought. So over the next year I gave several dozen talks, but I soon found the money was numbing my critical judgment—and my conscience.

TCPR: How so?

Dr. Carlat: The industry leaves nothing to chance. They measured how many extra Effexor prescriptions the doctors wrote after each of my talks. The higher the numbers, the more they put me on the podium. But there were problems with the drug, like hypertension and discontinuation symptoms. I was supposed to minimize the problems and emphasize the benefits, and there were problems with those benefits as well. Michael Thase had written a meta-analysis showing higher remission rates with Effexor than the SSRIs—45% vs 35%. It sounded good, but many of the studies in the analysis enrolled patients who had already failed an SSRI, which tipped the odds in favor of an antidepressant with a different mechanism of action like an SNRI (Thase ME et al, *Br J Psychiatry* 2001;178:234–241).

Carlat Print Publications	
Carlat Journal	**Editor-in-Chief**
Psychiatry Report (General Psychiatry)	Chris Aiken, MD
Addiction Treatment Report	Noah Capurso, MD
Child Psychiatry Report	Joshua D. Feder, MD
Geriatric Psychiatry Report	Stephanie Collier, MD, MPH
Hospital Psychiatry Report	Victoria Hendrick, MD

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TCPR: Wyeth marketed that study pretty heavily at the time, right?

Dr. Carlat: Yes, and I was part of that, until my conscience started tweaking me. At one talk, I told the docs that it was unclear whether Effexor was more effective than the SSRIs. A couple days later, the Wyeth district manager came by my office and said, "Dr. Carlat, you didn't seem as enthusiastic about the product at your last talk. Have you been sick?" It was at that moment that I decided to resign and start a publication that would counter the hype. A few months later, the first issue of *The Carlat Report* came out.

TCPR: How did the industry respond?

Dr. Carlat: I didn't accept industry funding because I didn't want them to interfere, but that didn't stop them. In 2004, I published an article on Cymbalta that criticized the industry for cherry-picking outcomes that favored their product. They used a novel method to account for dropouts, the "probability of response," which is less direct than the usual "last observation carried forward" method (Goldstein DJ et al, *J Clin Psychiatry* 2002;63(3):225–231). Soon after, our CME provider received a threatening fax from an Eli Lilly lawyer complaining that the article was inaccurate and unfair. We were running on a slim budget, and this nearly caused us to lose our CME accreditation and shut down.

TCPR: How did you handle it?

Dr. Carlat: I published their letter and my response on our website. I invited them to submit a rebuttal, which they did, and I published the rebuttal as well to ultimately let the readers decide. In the end it just shined a light on the problem of how the industry was managing statistics, which brought more readers in.

TCPR: Has the industry changed since then?

Dr. Carlat: One of the biggest changes came along with the Affordable Care Act in 2010, which contained a provision called the Physician Payments Sunshine Act. That required all pharmaceutical companies to publish their payments to doctors—money, research funding, lunches, textbooks, any transfer of value—on a government website called Open Payments.

TCPR: Has Open Payments made a difference?

Dr. Carlat: Yes. There's been a modest but consistent decline in the percentage of doctors accepting payments, particularly among psychiatrists. When Open Payments was launched, about half of all doctors received payments from the pharmaceutical industry. By 2018, that figure fell by 14% for all physicians and by 24% for psychiatrists (Marshall DC et al, *JAMA* 2020;324(17):1785–1788). My hunch is that doctors are not happy about their patients being able to look up that they've received free lunches from the industry.

TCPR: Sounds like a good thing, but does it change prescribing?

Dr. Carlat: I think so. A recent study showed that physicians are 58% more likely to prescribe a drug after receiving a payment from the company linked to that drug (www.tinyurl.com/564sjue9). And it doesn't have to be a big gift. Small gifts change prescribing patterns almost as much as large ones (DeJong C et al, *JAMA Intern Med* 2016;176(8):1114–1122). I think it has to do with something basic in our human nature. We want to do something in return when someone gives us something.

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Expert Interview
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TCPR: What about samples? Don't those help patients?

Dr. Carlat: The industry spends over $5 billion a year on samples. They aren't spending that money to help patients. They are spending it to increase the sales of brand-name drugs, and that adds unnecessary costs to the healthcare system (Lahey T, *Clin Transl Gastroenterol* 2014;5(12):e67). Most of the samples they give out are for chronic conditions. I'm not sure how helpful it is to give two weeks of free samples for a product that will cost the patient more in the long term.

TCPR: Are there brand-name drugs that offer something unique?

Dr. Carlat: Yes. One example is paliperidone (Invega). This antipsychotic was originally marketed for reasons that I did not find very convincing. It lacked drug interactions. It did not require dose titration, and it had FDA approval in schizoaffective disorder. My view has changed now that paliperidone is available as a six-month injection (Invega Hafyera). That's an advantage over other injectables that have to be given every two to six weeks. I'm more likely to start the oral, generic paliperidone when treating schizophrenia, knowing that the six-month product is out there if we need it.

TCPR: I'd like to ask you about some controversies in psychiatry. To start with, genetic testing.

Dr. Carlat: It sounded like a good idea at first. The problem is that every blinded, controlled trial of these tests produces negative results. That includes popular tests like GeneSight, Genecept, NeuroIDgenetix, and Neuropharmagen. If you read the abstracts, the studies sound positive, but that's only after data-fishing for any positive signal, and even then, the difference is barely detectable. That's not very convincing, especially considering these studies only enroll patients who are most likely to benefit from pharmacogenomic testing—the ones who did not respond to their first antidepressant.

TCPR: We've seen a rise in adult ADHD over the past 20 years. What are your thoughts on that?

Dr. Carlat: DSM-5 made adult ADHD easier to diagnose because it changed the required onset of symptoms from age 7 to age 12. It's also easy for patients to mimic the symptoms, and there are many adults with ADHD-like symptoms that are better explained by other causes, like sleep deprivation, head injuries, and other psychiatric disorders. On the other hand, we've all seen patients whose lives are changed after starting a stimulant in adulthood.

"Physicians are 58% more likely to prescribe a drug after receiving a payment from the company linked to that drug. And it doesn't have to be a big gift. Small gifts change prescribing patterns almost as much as large ones."

Daniel Carlat, MD

TCPR: What about transcranial magnetic stimulation (TMS)?

Dr. Carlat: That's one topic where my opinion has changed. When TMS first came out in 2008, it looked like it was not very effective, with response rates of 30% vs 20% for placebo. The FDA only approved it for patients who had failed one antidepressant trial, not two trials (which reflects true treatment resistance). But since then, it has gained FDA approval for treatment-resistant depression, and now I think TMS has a valid role. It works as well or better than medication, with fewer side effects. TMS also has new protocols that look even more effective, like the recently approved SAINT protocol that delivers TMS through intensive, all-day sessions over five days instead of spacing it out over six weeks (Cole EJ et al, *Am J Psychiatry* 2022;179(2):132–141).

TCPR: Thoughts on ketamine?

Dr. Carlat: Ketamine works quickly, but what's not clear is how to keep people well after they get better on it. Several medications, including lithium, have been tested to see if they sustain the response, but the only study I've seen that was positive involved cognitive behavioral therapy, not medication (Wilkinson ST et al, *Psychother Psychosom* 2021;90(5):318–327). Another thing that's not clear is whether the FDA-approved version—intranasal esketamine (Spravato)—is as effective as the original IV ketamine. In the clinical trials, the IV version had a much larger effect, but it's hard to compare the two across different studies. I'm only aware of one small trial that compared them head-to-head, and it didn't find any difference (Bahji A et al, *J Affect Disord* 2021;278:542–555; Correia-Melo FS et al, *J Affect Disord* 2020;264:527–534).

TCPR: What do you see in psychiatry's future?

Dr. Carlat: I'd like to see new treatments come out, but mostly we have repurposed medications in the pipeline. Many of them were once drugs of abuse, like the psychedelics. But I'm not discounting them. The psychedelic drugs look promising for treatment-resistant conditions. Psilocybin has a Phase III trial underway in treatment-resistant depression, and positive trials are already out for MDMA in treatment-resistant PTSD (Illingworth BJ et al, *J Psychopharmacol* 2021;35(5):501–511). But it's not just the drugs. In each of those trials, the dose was combined with a specific psychotherapy to enhance the response.

TCPR: Are you concerned about the potential for abuse with ketamine and the psychedelics?

Dr. Carlat: Certainly some will become used for nonindicated purposes. Regulation will curb a lot of that. So far, these drugs can only be dispensed through a REMS system and have to be delivered in a supervised office setting.

TCPR: What makes *The Carlat Report* unique?

Dr. Carlat: Well, we're not the only publication that doesn't accept outside funding. *Simple and Practical* and *Up to Date* also don't take industry money. What sets us apart is that we make sure the people who write for us or sit for interviews don't have industry ties. We also keep the pieces practical, easy to read, and—when possible—fun. That means cutting out all the literary "throat-clearing" that a lot of academic articles begin with, like "Major depressive disorder

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Viibryd Goes Generic, But Is It Worth Prescribing?

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Faster onset?

Vilazodone's clinical efficacy rests on four large, short-term randomized controlled trials in major depression. In the first trial, it separated from placebo at one week, and in another it separated at two weeks. However, there was no early response in the remaining two trials, and most antidepressants have some evidence of early efficacy within the first two weeks, so even a generous interpretation here does not suggest that anything special is going on (Chauhan M et al, *Neuropsychiatr Dis Treat* 2022;18:1175–1193).

Nor do any of the vilazodone trials suggest greater potency than other medications. Its antidepressant effects were similar to those of citalopram 40 mg/day in a large head-to-head trial of 1,133 patients. That study also compared two fixed doses of vilazodone (20 mg and 40 mg) and found no evidence of greater benefits at the higher dose (Mathews M et al, *Int Clin Psychopharmacol* 2015;30(2):67–74).

Overall, vilazodone's efficacy is similar to that of other modern-day antidepressants, which is not particularly high. The number of patients needed to treat (NNT) to achieve a response with vilazodone that wouldn't have been seen with a placebo is 8, compared to 4–16 for other antidepressants—with a lower NNT indicating greater efficacy (Citrome L, *J Affect Disord* 2016;196:225–233). Whether vilazodone can reliably bring patients to full remission is debatable. A meta-analysis suggests that 10% of patients achieve remission on vilazodone, but the only large trial that reported remission rates found it was no better than placebo (Khan A et al, *J Clin Psychiatry* 2011;72(4):441–447).

Vilazodone has never been tested in treatment-resistant depression, but two "switch" studies in patients who failed to recover after a trial of an SSRI or SNRI cast doubt about its ability to work when other antidepressants have not. Its long-term data are also uninspiring. Vilazodone failed to prevent depression in a large study that randomized patients who responded to the drug to either placebo or continuation. That is telling, since these "enriched" study designs usually favor the antidepressant (Chauhan et al, 2022).

Better for anxiety?

With its resemblance to SSRIs and buspirone, vilazodone might seem well suited for anxiety disorders. However, its lack of FDA approval in anxiety disorders, despite industry-supported trials in generalized and social anxiety, raises doubts. Vilazodone did work in three large randomized controlled trials of generalized anxiety disorder (20–40 mg/day, mean 31 mg/day), but the effect size was small and its tolerability was poor in this population, particularly with nausea and diarrhea (Zareifopoulos N and Dylja I, *Asian J Psychiatr* 2017;26:115–122). An industry-sponsored social anxiety trial was positive, but the study was small and the dropout rate high. A larger follow-up study in social anxiety disorder was abandoned midstream.

The story brightens when we turn to anxious depression, but not enough to endorse vilazodone as a first-line option. Michael Thase and colleagues reanalyzed two large vilazodone trials to see if its effects differed in those with anxious vs nonanxious depression (the majority, 82%, fell into the anxious category). Vilazodone improved both anxiety and depression in the anxious group but did not work at all in those with nonanxious depression (Thase ME et al, *Int Clin Psychopharmacol* 2014;29(6):351–356). That almost sounds like an endorsement of vilazodone in anxious depression, except for this: A large trial found that citalopram was a more effective anxiolytic in depressed patients than vilazodone.

Better for sex?

When vilazodone was first launched, the initial data suggested the drug lacked sexual side effects. Later, we learned that most of the patients in those trials had nothing to lose, as their sex drive was already close to zero when they started vilazodone. While vilazodone did not lower their already absent libido, it did cause sexual dysfunction in those who entered the study with their sex drives intact (at a rate of 8% vs 1% on placebo). Later head-to-head comparisons with sertraline and paroxetine suggested that vilazodone carries a lower risk of sexual dysfunction than the SSRIs, consistent with the partially supported idea that buspirone treats SSRI-induced sexual dysfunction (Chauhan et al, 2022).

Vilazodone: Quick Facts	
Benefits	FDA approved in major depression. Small benefits in generalized anxiety disorder.
Dosing	Start 10 mg/day, increase to 20 mg/day after one week. If no response after three to six weeks, increase to max of 40 mg/day. Take with food (taking without food reduces levels by 50%). Take in morning as it may be activating.
Drug Interactions	Avoid with MAOIs. Vilazodone's levels are raised by CYP3A4 inhibitors (eg, grapefruit juice) and lowered by CYP3A4 inducers (eg, modafinil). May raise tricyclic and antipsychotic levels (moderate CYP2D6 and CYP2C19 inhibitor).
Risks	Similar to SSRIs (nausea, dizziness, insomnia; potential hyponatremia and osteopenia) but lower risk of sexual dysfunction.

Tolerability

Overall, vilazodone's tolerability problems are similar to those of the SSRIs, with transient nausea, diarrhea, dizziness, and more lasting sexual dysfunction and insomnia. There is no reason to think that vilazodone is free of more serious SSRI side effects like hyponatremia, osteopenia, suicidality, and withdrawal problems, but research into these areas is scant.

How to use it

Vilazodone dosing is relatively straightforward, with a few obstacles that are described in the table. For example, it needs to be taken with food—up to half the dose goes unabsorbed in a fasted state. On the other hand, potent CYP3A4 inhibitors, such as grapefruit juice, can raise vilazodone levels about two-fold.

CARLAT VERDICT

Consider vilazodone in patients who respond to an SSRI but need an antidepressant with a lower risk of sexual side effects, and who do not respond to bupropion and vortioxetine (where sexual side effects are closer to zero). Otherwise, there are several reasons to avoid this antidepressant first line: tolerability, food interactions, and questionable benefits when it comes to preventing depression or treating comorbid anxiety disorders.

Research Updates IN PSYCHIATRY

PSYCHOSIS

Aripiprazole-Related Psychotic Exacerbations

Brian Miller, MD, PhD, MPH. Dr. Miller, author of this educational activity, receives research support from Augusta University, the National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute. Relevant financial relationships listed for the author have been mitigated.

REVIEW OF: Ma C-H et al, *Ther Adv Psychopharmacol* 2022;12:1–10

STUDY TYPE: Randomized controlled trial

Aripiprazole has a unique mechanism of action. It is a partial agonist at the D2 receptor, and this has raised concerns that psychosis may worsen when switching to this drug from a full D2 antagonist. Observational studies of aripiprazole switches have also supported this idea, and this paper is the first controlled trial to examine aripiprazole-related exacerbations.

This study reanalyzed an eight-week, open-label, randomized controlled trial of switching from other oral antipsychotics to aripiprazole. Seventy-nine adults (mean age 39) with schizophrenia/schizoaffective disorder were switched to aripiprazole 15 mg due to intolerable adverse effects or inadequate therapeutic effect of their current antipsychotic. Most were clinically stable with symptoms in the mild range (average PANSS score = 55). After two weeks of aripiprazole, subjects were randomized to taper their pre-switch antipsychotic over one (n = 38) or four (n = 41) weeks. Aripiprazole-related exacerbation was defined as an increase of ≥2 points on the four PANSS hallucination/delusion items within 28 days of starting aripiprazole.

Twenty-one (27%) subjects had an aripiprazole-related exacerbation and 46 (58%) did not. Most of the exacerbations (62%) occurred within the first week after switching. Compared to those who did not worsen with the switch, those who did had a higher baseline antipsychotic dose (406 vs 268 chlorpromazine equivalents) and were more likely to be taking first-generation antipsychotics (62% vs 35%). However, after controlling for age and sex, only the baseline antipsychotic dose remained a significant predictor of aripiprazole-related exacerbations.

Although the rates of aripiprazole-related exacerbations are high, we don't know if this phenomenon is unique to aripiprazole because the study did not test switches to other antipsychotics.

CARLAT TAKE

Watch for worsening of psychosis when switching to aripiprazole, particularly when the patient starts the cross-taper on high doses of an antipsychotic or first-generation antipsychotics.

DEPRESSION

Should We Use Two Antidepressants to Treat Unipolar Depression?

Paul Riordan, MD. Dr. Riordan has no financial relationships with companies related to this material.

REVIEW OF: Henssler J et al, *JAMA Psychiatry* 2022;79(4):300–312

STUDY TYPE: Meta-analysis of randomized trials

Guidelines recommend a single antidepressant for nonpsychotic major depressive disorder, but is this the most effective approach? Or should we combine two antidepressants into a synergistic combination where the sum is greater than the parts? This meta-analysis seeks to answer these questions.

The authors identified 39 randomized trials lasting 3–12 weeks that compared dual antidepressant therapy to monotherapy for 6,751 patients with unipolar depression. They excluded maintenance trials. The primary outcome was the standardized mean difference (SMD, also known as effect size) of combination therapy compared to monotherapy. Secondary outcomes included remission rates, response rates, overall dropout rates, and dropout rates due to adverse events. The authors also performed several subgroup analyses to determine which combination of antidepressants worked best.

Overall, there was a small benefit to combination therapy relative to monotherapy with an SMD of 0.31 (95% confidence interval [CI], 0.19–0.44), which roughly translates to a number needed to treat of 8–10. For the secondary outcomes, there was a 52% increase in odds of remission and a 40% increase in odds of response. Notably, there were no differences in the rates of overall dropouts or dropouts due to adverse events.

So which combination should we use? Bupropion combinations failed to do better than monotherapy (SMD = 0.10; 95% CI, -0.07–0.27), while combinations involving the presynaptic α2-autoreceptors (specifically, augmentation with mirtazapine 7.5–45 mg/day, trazodone 100 mg/day, and mianserin 30–60 mg/day) did separate from placebo. The α2-autoreceptors were particularly effective when paired with an SSRI, SNRI, or tricyclic antidepressant (SMD = 0.37; 95% CI, 0.19–0.55). The authors suggest this combination as first-line treatment for severe cases of depression and for patients who do not respond to monotherapy.

These results conflict with other meta-analyses, which did not find a significant effect for mirtazapine augmentation, and the difference may lie in how the data were grouped (Zhou X et al, *J Clin Psychiatry* 2015;76(4):e487–e498). Nearly all of the large studies for the α2-autoreceptors were negative, while the positive results that tilted the balance came almost entirely from small studies involving fewer than 100 subjects. Specifically, all six large trials of mirtazapine augmentation were negative, as was the single large trial of mianserin augmentation. The two trazodone studies used a low dose of 100 mg, which is

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more in line with its use as a hypnotic than its antidepressant dose range, and neither of the studies tested the augmentation against placebo.

While these results paint a mixed picture of mirtazapine in depression, there is evidence that mirtazapine augmentation helps associated symptoms of insomnia and anxiety (Rifkin-Zybutz R et al, *J Psychopharmacol* 2020;34(12):1342–1349).

CARLAT TAKE

Although this analysis finds a ray of hope for antidepressant combinations involving mirtazapine, trazodone, or the non-US antidepressant mianserin, that optimism is tempered by the negative results of large controlled trials. In practice, trazodone and mirtazapine may work best for associated symptoms of insomnia or—in the case of mirtazapine—anxiety.

PSYCHOTHERAPY

DBT Skills May Reduce Polypharmacy in Borderline Personality Disorder

Simon M. Dosovitz, MD. Dr. Dosovitz has no financial relationships with companies related to this material.

REVIEW OF: Soler J et al, *Acta Psychiatr Scand* 2022;145:332–342

STUDY TYPE: Retrospective cohort study

Polypharmacy is common in borderline personality disorder (BPD), despite the underwhelming evidence for this practice. Psychotherapy is first line for this disorder, and there is compelling support for dialectical behavior therapy (DBT), transference-focused therapy, and mentalization-based therapy. This study examines skills training, one component of DBT treatment, and tests whether it can reduce the use of psychotropics in BPD.

The authors examined the charts of 377 patients admitted to a specialized clinical service at a large academic medical center in Barcelona, Spain. All patients on this service had their diagnosis of BPD confirmed using instruments such as the Structured Clinical Interview for DSM and were provided with psychoeducation and medication management. In addition, patients could elect to participate in the DBT skills training (DBT-ST) group. Out of the entire sample, 182 participated, while 195 did not. Both groups were predominantly female, in their late 20s to early 30s, and had multiple psychiatric comorbidities. Symptom severity was higher among DBT-ST participants, and more of these patients were on three or more medications or were prescribed benzodiazepines. The number of medications (2.14–2.66) was not significantly different between groups.

During the course of treatment, patients who completed DBT-ST decreased the average number of medications they were taking from 2.66 to 1.95, while those in the control group did not see a decrease. Most significantly, the DBT-ST participants had a reduction in benzodiazepine usage, with the percentage of patients using these medications decreasing from 54% to 27%. Antipsychotic and mood stabilizer use were also lower after the intervention among the DBT-ST participants. Antidepressant usage did not change in either group, and functional outcomes (including symptom severity) were not measured.

There are various limitations inherent in any retrospective, uncontrolled study such as this one. Most importantly, patients were not randomly assigned to skills training, but participated based on preference. The decision to start DBT-ST might have reflected a greater motivation to change treatments and a preference for psychotherapy over pharmacotherapy—which could explain the decrease in medication use.

CARLAT TAKE

Design limitations of this study aside, we are encouraged that an educational therapy—one with a focus on emotion regulation and easy deliverability in a group format—might help patients reduce psychiatric polypharmacy and benzodiazepine use.

SCHIZOPHRENIA

Pimavanserin Improves Negative Symptoms of Schizophrenia

Brian Miller, MD, PhD, MPH. Dr. Miller, author of this educational activity, receives research support from Augusta University, the National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute. Relevant financial relationships listed for the author have been mitigated.

REVIEW OF: Bugarski-Kirola D et al, *Lancet Psychiatry* 2022;9(1):46–58

STUDY TYPE: Randomized placebo-controlled trial

Negative symptoms of schizophrenia—including apathy, asociality, and blunted affect—predict disease burden and are difficult to treat. We lack FDA-approved therapies, and we don't know whether antipsychotics with novel mechanisms of action have efficacy for negative symptoms. Pimavanserin (Nuplazid) is a novel antipsychotic approved for psychotic symptoms in Parkinson's disease. Rather than antagonizing the dopamine D2 receptor, pimavanserin appears to work by blocking the 5-HT2A receptor, where it is both an antagonist and an inverse agonist (as an antagonist, it blocks the receptor; as an inverse agonist, it binds to the receptor and induces the opposite effects as an agonist). An earlier trial found benefits for pimavanserin augmentation in major depression (Fava M et al, *J Clin Psychiatry* 2019;80(6):19m12928), and the current study is the first to test pimavanserin augmentation for negative symptoms of schizophrenia.

This was a randomized, double-blind, placebo-controlled trial of pimavanserin as an adjunct to ongoing antipsychotic medication, in 403 stable adult outpatients ages 18–55 (mean 38) with schizophrenia and predominant negative symptoms in North America and Europe (specifically, patients scored at least 20 on the negative symptom domain of the Positive and Negative Syndrome Scale [PANSS]). Patients

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CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com to take the post-test. You will be given two attempts to pass the test. You must answer 75% of the questions correctly to earn credit. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives are listed on page 1.

1. Which of the following antidepressants was found to carry the lowest risk of sexual dysfunction according to a 2022 review (LO #1)?
   - [ ] a. Sertraline
   - [ ] b. Vilazodone
   - [ ] c. Paroxetine
   - [ ] d. They all carry an equal risk of sexual dysfunction

2. According to Dr. Carlat, how do payments or gifts from a pharmaceutical company influence how clinicians prescribe the company's drug (LO #2)?
   - [ ] a. Gifts only change prescribing behaviors when accompanied by educational material on the product
   - [ ] b. Small gifts have little to no effect on clinicians' prescribing patterns
   - [ ] c. Physicians are 10% more likely to prescribe the company's drug after receiving a payment or gift from them
   - [ ] d. Small gifts change prescribing patterns almost as much as large gifts

3. According to a 2022 study of adults with stable, chronic schizophrenia, adjunctive pimavanserin reduced negative symptoms in patients with what effect size (LO #3)?
   - [ ] a. Small
   - [ ] b. Medium
   - [ ] c. Large
   - [ ] d. Pimavanserin did not separate from placebo

4. What statement reflects the available research on vilazodone in depression (LO #1)?
   - [ ] a. After one week, vilazodone separated from placebo in all four clinical trials
   - [ ] b. Vilazodone outperformed citalopram in a head-to-head trial
   - [ ] c. In vilazodone responders, continuation did not prevent depression compared to placebo
   - [ ] d. Compared to placebo, vilazodone has a number needed to treat of 3

5. According to Dr. Carlat, the newly approved SAINT protocol for transcranial magnetic stimulation appears even more effective than previously used protocols for treatment-resistant depression (LO #2).
   - [ ] a. True
   - [ ] b. False

Research Updates

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were treated with either pimavanserin (starting dose 20 mg daily, dose range 10–34 mg daily) or placebo, in addition to their current antipsychotic, for 26 weeks. The primary outcome was change in the Negative Symptom Assessment (NSA-16) from baseline to week 26. The secondary endpoint was change in the Personal and Social Performance (PSP) scale, which assesses functioning in four areas: socially useful activities; personal and social relationships; self-care; and disturbing and aggressive behaviors. A total of 86% of subjects completed the trial.

After 26 weeks, the pimavanserin group showed a significantly greater reduction in negative symptoms versus placebo (-10.4 vs -8.5 points on the NSA-16), corresponding to a small effect size (0.21), but no change in PSP score (difference 0.0). In post-hoc analyses, the effect size for the NSA-16 was greater in patients who received the 34 mg dose of pimavanserin (0.34), as well as in men, patients from Europe, and patients with chronic negative symptoms (lasting longer than five years). Adverse effects were similar between study groups (35%–40%), most commonly headache and somnolence, and were typically mild. Pimavanserin was associated with a modest but statistically significant increase in the QT interval as compared to placebo (4.5 vs 0.0 ms). There were no clinically relevant effects of pimavanserin on vital signs, weight, glucose, or lipids in this six-month study.

Potential limitations included the flexible dosing schedule, as only 54% of patients were increased to a 34 mg pimavanserin dose. The study participants were stable outpatients with chronic schizophrenia who primarily suffered from negative symptoms, which may limit the generalizability of the study findings. We also don't know whether response to pimavanserin will vary depending on the antipsychotic it is combined with.

CARLAT TAKE

Adjunctive pimavanserin may improve negative symptoms in patients with stable, chronic schizophrenia. However, the overall effect is small, and the price of the medication is high ($4,000 monthly).

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Expert Interview
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affects 17 million adults and is a leading cause of work-related disability worldwide." I don't think our audience needs to be told the same things over and over.

TCPR: What's in the future for *The Carlat Report?*

Dr. Carlat: We're releasing a series of short books, starting with one on treatments for alcohol use disorder. Those books will be paired with videos showing how we'd talk to patients about the treatments. We also have a new webinar series of 30-minute CME videos on focused topics like choosing a stimulant in ADHD and managing depression in the peripartum period. We've added more specialty newsletters recently—geriatric psychiatry, hospital psychiatry (see the table, Carlat Print Publications, on page 2)—and we're thinking of adding more, like psychotherapy and interventional psychiatry.

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

❖ ❖ ❖

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