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Daniel Carlat, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Antidepressant Roundup

Learning Objectives
After reading these articles, you should be able to:
1. Describe some of the pharmacologic approaches to treatment-resistant depression.
2. Evaluate the effectiveness of the newer drugs vilazodone (Viibryd), levomilnacipran (Fetzima), vortioxetine (Brintellix), and ketamine in treating depression.
3. Determine the effectiveness of using light therapy to treat non-seasonal depression.

Four Newer Antidepressants: Should You Use Them?

Steve Balt, MD
Psychiatrist in private practice, San Francisco Bay Area

Talia Puzantian, PharmD, BCPP
Deputy editor, The Carlat Psychiatry Report, *and associate professor at the Keck Graduate Institute School of Pharmacy in Claremont, CA*

Dr. Balt discloses that his spouse is employed as a sales representative for Otsuka America. Dr. Puzantian discloses that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

In Summary

- Vilazodone has not been proven more effective than other antidepressants in treating depressed patients with significant anxiety.
- It is unclear if levomilnacipran has clear efficacy advantages compared to other SNRIs.
- Based on the results of cognitive studies, the company that manufactures vortioxetine has applied for (and been denied) FDA approval of a new "cognitive dysfunction in MDD" indication.
- The antidepressant effects of ketamine are short-lived, and its serious side effects require inconvenient, doctor-monitored intravenous admission.

Since 2011, 3 new antidepressants have been approved by the FDA, and another (ketamine) has been generating buzz as a potential off-label medication for depression. In this article, we'll take a step back and review the data on vilazodone (Viibryd), levomilnacipran (Fetzima), vortioxetine (Brintellix), and ketamine.

Vilazodone (Viibryd)

Vilazodone was approved by the FDA in January of 2011, making it the oldest of the newer antidepressants. Those who like tracking mechanisms of action are calling vilazodone a "SPARI," which stands for serotonin partial agonist/reuptake inhibitor. The drug inhibits reuptake of serotonin (like SSRIs) and has partial agonism at 5-HT1A receptors (like buspirone). So, theoretically, giving your patients vilazodone is similar to giving them both an SSRI and buspirone

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Q&A With the Expert

Thinking Creatively About Treatment-Resistant Depression

J. Alexander Bodkin, MD

Director of the Clinical Psychopharmacology Research Program at McLean Hospital in Belmont, MA; assistant professor of psychiatry at Harvard Medical School

Dr. Bodkin has disclosed that he has been a principal investigator in a study of brexpiprazole. Dr. Carlat has reviewed his interview and has found no evidence of bias in this educational activity.

TCPR: The term "treatment-resistant depression" is sort of thrown around a bit. I'm sure that there are various formal or informal definitions of it, but how do you think about it?
Dr. Bodkin: The formal definition basically requires 2 failures of distinctly different antidepressants at robust doses for adequate duration. But personally, I think it is important to look at the type of depression before you start talking about whether or not it is treatment resistant. In other words, not just does your patient meet the criteria for depression, but what does the depression look like?

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at the same time. Is that a good thing? Nobody knows for sure. In the STAR*D trial, buspirone had a cameo appearance in one of the steps, being used as an augmenter of citalopram, and it worked as well as bupropion augmentation—a finding that may or may not have any relevance to vilazodone.

When the drug was first approved, the word on the street was that it (1) may work faster than other antidepressants, (2) may have fewer sexual side effects, and (3) may be more effective for anxiety. We were skeptical of these claims then, as was the FDA (see *TCPR,* April 2011 and http://carlatpsychiatry.blogspot.com/2011/10/fda-slams-viibryd-better-sexual-profile.html). But new data have accumulated since then. We'll rely mainly on a review published in 2015, which included 4 later-stage and post-marketing studies, as opposed to the pre-approval studies that the FDA reviews (Hellerstein DJ et al, *Core Evid* 2015;10:49–62).

TCPR Note: In the January 2016 issue, the correct code for moderate alcohol use disorder in the ICD-10 Conversions for Common Diagnoses table (p. 6) is 303.90. We apologize for any inconvenience.

Onset of action

The idea of faster onset of action was originally based on one piece of animal data and one piece of human data. The animal data showed that vilazodone quickly enhanced serotonin transmission in rats via 2 distinct mechanisms: 5-HT1A partial agonism and regular serotonin reuptake. In the human study, vilazodone showed statistically significant reduction in depression scores compared to placebo quite early, by week 1, although there was no active drug comparison (Rickels K et al, *J Clin Psychiatry* 2009;70(3):326–333).

Two more recent studies showed greater improvement versus placebo as early as week 2 (Croft HA et al, *J Clin Psychiatry* 2014;75(11):e1291–e1298; Mathews M et al, *Int Clin Psychopharmacol* 2015;30(2):67–74). However, antidepressant response at 2 weeks is not unique to vilazodone. Early improvement is the rule and not the exception for many antidepressants (Szegedi A et al, *J Clin Psychiatry* 2009;70(3):344–353). In addition, when researchers focused on remission instead of response, vilazodone took 6 full weeks to outperform placebo. The bottom line is that there is no convincing evidence that vilazodone has a faster onset of action than any of its competitors.

Sexual side effects

Early studies suggesting a cleaner sexual side effect profile for vilazodone were problematic. First, there was no SSRI comparator, which would have been necessary to make any claims that vilazodone had an advantage over other agents. Second, most of the patients enrolled had preexisting sexual dysfunction before being randomized to vilazodone or placebo. One can argue that this design has the advantage of being generalizable to many of our patients, who have underlying sexual dysfunction due to depression or age, for example. On the other hand, it's akin to testing whether a drug has a headache side effect by giving it to a bunch of people who already had headaches. Any new-onset headaches would be obscured by the pathology already there. And indeed, in the company-funded study, treatment with vilazodone didn't worsen the already high burden of sexual side effects—in fact, it was no different from placebo, both of which resulted in a slight improvement in sexual functioning (Rickels K et al, *J Clin Psychiatry* 2009;70(3):326–333).

In a more recent industry-funded post-hoc analysis of patients with normal baseline sexual function who were randomized to vilazodone, citalopram, or placebo, there were no significant differences in onset of new sexual side effects. The rates were: placebo: 12%; vilazodone 20 mg/day: 16%; vilazodone 40 mg/day: 15%; and citalopram 40 mg/day: 17% (Mathews MG et al, *Abstract 45*, ASCP 2014; http://ascpmeeting.org/wp-content/uploads/2014/06/Poster-Abstracts-FINAL.pdf). There was also no significant difference among those who had baseline sexual dysfunction: 33% of patients on placebo, 35% on vilazodone 20 mg/day, 30% on vilazodone 40 mg/day, and 28% on citalopram patients improved to normal sexual function by the end of the study.

According to the website ClinicalTrials.gov, there are ongoing studies of vilazodone addressing the sexual function issue. Until those results are published, we continue to consider the low sexual side effect claims as unsubstantiated.

Efficacy in anxiety

There's a theoretical argument to be made that vilazodone's 5-HT1A partial agonism might give it special anti-anxiety power. The only clinical trial evidence thus far is based on comparisons with placebo. As is true for many other antidepressants, vilazodone reduces scores on the Hamilton Anxiety Rating Scale more than placebo (Rickels K et al, *J Clin Psychiatry* 2009;70(3):326–333; Khan A et al, *J Clin Psychiatr* 2011;72(4):441–447). Another analysis of these data found that vilazodone may be more effective for the subgroup of anxious depressed patients than for the non-anxious depressed (Thase ME et al, *Int Clin Psychopharmacol* 2014;29(6):351–356). Promising, but

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we'd need data comparing this medication with other antidepressants to be convinced that it has an advantage.

TCPR Verdict: Based on this second look at vilazodone, we don't see any new evidence that it works faster, has fewer sexual side effects, or is preferred in depressed patients with significant anxiety. We consider this a second-line antidepressant to be used after generics have failed.

Levomilnacipran (Fetzima)

Levomilnacipran was approved by the FDA in July 2013 for major depressive disorder. It is the close chemical cousin (an enantiomer) of milnacipran (Savella), approved in the U.S. in 2009 for fibromyalgia and approved for depression in other countries. Levomilnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI), which puts it in the same class as duloxetine (Cymbalta), venlafaxine (Effexor XR), and desvenlafaxine (Pristiq). However, levomilnacipran is more selective for inhibiting norepinephrine reuptake than the others—studies have shown that it has a 15-fold higher selectivity for norepinephrine than for serotonin. This selectivity disappears at higher doses.

But does norepinephrine selectivity mean anything clinically? Some researchers have hypothesized that there is a "norepinephrine deficit depression," associated with poor concentration, inattention, low motivation, lack of energy, and cognitive impairment. This might be distinct from a "serotonin deficit depression," more associated with anxiety, appetite disturbances, and suicidality (Moret C et al, *Neuropsychiatr Dis Treat* 2011;7Suppl1:9–13; Nutt DJ, *J Clin Psychiatry* 2008;69SupplE1:4–7). It would be nice if we could someday identify depressive subtypes that respond to specific medications, but the evidence for this norepinephrine/serotonin division is still indirect and preliminary.

Nonetheless, these speculations provide promotional talking points for reps, who may argue that their drug has a special norepinephrine-based power to improve impaired daily functioning. Let's look at the data.

Evidence on improving functioning

According to a recent meta-analysis, 4 out of 5 double-blind, placebo-controlled, short-term studies found that levomilnacipran was more effective than placebo for overall depressive symptoms (Montgomery SA et al, *CNS Spectr* 2014;5:1–9). The average response rate was 46% for levomilnacipran (vs. 36% on placebo) and the average remission rate was 28% (vs. 22% on placebo).

These studies also assessed change in functionality as a secondary measure. This was done using the Sheehan Disability Scale (SDS), a self-rating scale which asks about work/school, social life, and family life to measure functionality (http://www.cqaimh.org/pdf/tool_lof_sds.pdf). Each of the three domains is scored from 0 (unimpaired) to 10 (extremely impaired). Any domain with a score of 5 or higher means significant functional impairment. So an SDS score of ≤12 total and ≤4 on all subscales indicates functional responders. An SDS score of ≤6 total and ≤2 on all subscales means functional remitters.

The meta-analysis reported a mean change in SDS score that was significantly greater with levomilnacipran compared to placebo but the actual difference in score was small, only a mean of 2.2 points better than placebo, (Sambunaris A et al, *Int Clin Psychopharmacol* 2014;29(4):197–205). The pooled response rate—that is, the percent of patients who functioned better at the end of the trial—was 39% for levomilnacipran vs. 29% on placebo, and the pooled remission rate was 22% vs. 15% on placebo.

Of course, the skeptic in us points out that any medication that eases depression is likely to also improve functioning. It may be that all antidepressants, regardless of their mechanisms of action, are just as effective as levomilnacipran for impaired functioning. Unfortunately, the company has not compared its drug with anything more robust than placebo, so we don't know the answer yet.

An interesting secondary, post-hoc analysis of 1 of the 10-week placebo-controlled levomilnacipran studies looked at individual items in the major depression scales. The results didn't support that levomilnacipran was better at any particular neurotransmitter profile of symptoms. Instead, the drug improved the same types of symptoms targeted by other antidepressants. So it's unclear whether the higher selectivity for norepinephrine truly relates with any significant clinical outcome (Montgomery SA et al, *Int Clin Psychopharmacol* 2014;29(1):26–35).

TCPR Verdict: Levomilnacipran is an SNRI with especially strong reuptake inhibition of norepinephrine as opposed to serotonin. But whether it has any clear efficacy advantages over its competitors is not clear.

Vortioxetine (Brintellix)

Vortioxetine was approved by the FDA in September of 2013 for major depression. It's considered a "multimodal agent," meaning that it acts not only as a serotonin reuptake inhibitor but also affects several other serotonin receptors. It is an agonist of 5-HT1A receptors, a partial agonist at 5-HT1B receptors, and an antagonist at 5-HT3 and 5-HT7 receptors.

How well does vortioxetine work? A recent review of published and unpublished trials of the medication found 14 short-term randomized trials (6 to 12 weeks); eight of which were positive, five were negative, and one was considered "failed" because neither vortioxetine nor the active control, duloxetine, showed symptomatic improvement over placebo (Kelliny M et al, *Ther Clin Risk Management* 2015;11:1192–1212). Some studies compared vortioxetine to placebo, others to duloxetine or venlafaxine. Vortioxetine showed no clear superiority over active controls in measures of response or remission. So while vortioxetine has a distinctive pharmacological profile (Citrome L, *Int J Clin Pract* 2014;68(1):60–82), it is no more effective for core depressive symptoms than standard antidepressants.

The approved dose of vortioxetine is 10–20 mg/day. Sexual dysfunction has been reported to be minimal, but most premarketing trials relied solely on spontaneous reporting of adverse effects, which is known to underestimate their frequency (Cosgrove L et al, *Account Res* 2016 [Epub ahead of print]), and in one of the few trials that used a scale to measure effects on sexual performance, the authors concluded that "the sample number is too small to draw any conclusions"

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Expert Interview
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TCPR: How do you think about depression?

Dr. Bodkin: In my opinion, depressive illness is a final common pathway for a number of different brain problems. There are a whole range of ways to have 5 out of the 9 DSM symptoms. Some of them are highly genetic; some of them are less genetic; some of them seem not to be genetic at all; some of them seem to have to do with literal brain injury; some of them have to do with—shall we say—psychological injury, and many of these versions of depression overlap.

TCPR: What are some of the useful large categories of types of depression?

Dr. Bodkin: I ask myself the following questions as I'm evaluating and treating patients:

1. Does this patient have a bipolar illness? If so, that calls, at least to some extent, for a significantly distinct treatment approach.
2. Does this patient have melancholia? This is a clear acute-onset medical-looking depressive illness with loss of capacity for any emotional experience at all, reward or otherwise. We see this a relatively small percentage of the time in its pure form, but melancholia is an illness that has one set of best interventions.
3. Does this patient have a major depression with atypical features? What I mean by this is the capacity to be brought back to an emotionally normal or an undepressed state, at least briefly, by things in life going the right way. A patient might have a wonderful couple of days until a disappointment happens or a perceived affront, rejection, or failure. This is called mood reactivity and it is a requirement as far as a DSM diagnosis. About 15% of patients have atypical features (Seemüller F et al, *J Affect Disord* 2008;108(3):271–278).

"I think that the enormous overgrowth of the treatment resistant category has to do with the hesitancy in using the MAO inhibitors or tricyclics due to their side effects. Tricyclics, in particular, are great uptake inhibitors that cover not only serotonin and norepinephrine, but they are also to some extent antiadrenergic and anticholinergic."

J. Alexander Bodkin, MD

TCPR: What's the best treatment approach for depression with atypical features?

Dr. Bodkin: These are the patients who also tend to respond better to the monoamine oxidase inhibitors (MAOIs). But these medications are rarely used. In fact, one of the reasons I think we have this troublesome population of so-called treatment-resistant depressives is because by and large, nobody gets tried on MAOIs. And you can't really be said to be treatment resistant until you've been on the standard available treatments.

TCPR: Can you expand upon this?

Dr. Bodkin: Sure. I think that the enormous overgrowth of the treatment resistant category has to do with the hesitancy in using the MAO inhibitors or tricyclics due to their side effects. Tricyclics, in particular, are great uptake inhibitors that cover not only serotonin and norepinephrine, but they are also to some extent antiadrenergic and anticholinergic. We are learning more about how tricyclics may have downstream effects on both the opioid (Onali J et al, *Pharmacol Exp Ther* 2010;332(1):255–265) and dopamine (Menza M et al, *Neurology* 2009;72(10):886–892) pathways. The pure serotonin uptake-inhibiting drugs really only take one feature of these wonderful old dirty drugs and therefore are less effective for certain types of depression. In the STAR*D trial, only 28% of people adequately treated with an SSRI achieved remission (Trivedi MH et al, *Am J Psychiatry* 2006;163(1):28–40). That's a low rate of remission, and yet SSRIs remain the standard of care. My colleague and I did a review on the extensive published evidence for markedly greater efficacy of the TCAs relative to SSRIs (Bodkin JA and Goren JL, *Psychiatric Times* 2007; 24(11):20–32). The 2 most famous studies that we looked at were the Danish comparisons of clomipramine with citalopram (*Psychopharmacology* (Berl) 1986;90(1):131–138), and with paroxetine (*J Affect Disord* 1990;18(4):289–299). In our 2007 review, we also reviewed published evidence of the superior efficacy of MAOIs compared to SSRIs in 2 subgroups of depression patients: those with atypical features and those showing treatment resistance.

TCPR: Of course SSRIs are quite safe, which may be a reason why standard practice is to start with them.

Dr. Bodkin: This is a standard practice, and I do not think that it is sound. Multiple SSRI trials can be a terrible waste of valuable time for patients who are suffering. In general, the SSRIs are most effective in anxiety disorders. I choose SSRIs first for patients with somatic symptoms of panic, or sometimes for patients with a more generalized anxiety, people who are clearly stewing, worrying, ruminating, fretting, and anticipating problems. SSRIs are somewhat less effective in depressive disorders with prominent anxiety. Now, in patients with psychomotor retardation, deep apathy, anergia, lassitude, loss of drive, if you can ameliorate the anxiety component, these symptoms will get somewhat better in some patients, but you will really not achieve remission.

TCPR: So what do you do in this case?

Dr. Bodkin: If there is a partial response, generally the typical next step is to try to enhance that rather than stop the drug and begin with something else. If the prominent residual symptoms has to do with, let's say, insomnia or persistent loss of appetite, then you would add something that might ameliorate that, for example, mirtazapine. But if the problem is actually most prominently anergia, bupropion is very helpful (Bodkin J et al, *J Clin Psychiatry* 1997;58(4):137–145). Similarly, bupropion can help patients with a loss of sexual drive, whether from the depression itself or from an SSRI. Atypical antipsychotics have a place, and they can be remarkably helpful in treating what I call the "turbulent distress" experience, which can be anxiety, or anger, or both. Published evidence in this realm has focused primarily on quetiapine, which has been shown robustly effective in generalized anxiety disorder, a condition featuring "turbulent distress," both as an SSRI adjunct (Simon NM et al, *Psychopharmacology* (Berl) 2008;197(4);675–681) and as monotherapy (http://goo.gl/4XfxUa). Of course, people often gain weight on atypical antidepressants;

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(Mahableshwarkar AR et al, *J Clin Psychiatry* 2015;76(5):583–591).

Is vortioxetine a smart pill?

As we know, "diminished ability to think or concentrate" is one of the DSM-5 criteria for major depression. Specific domains such as executive function, processing speed, attention, and learning and memory, have been found to be deficient during acute major depressive disorder (MDD) (Hammar A and Ardal G, *Front Hum Neurosci* 2009;3:26).

In an effort to get a leg up on its competitors, the manufacturer has done studies showing that vortioxetine improves patients' performance on experimental cognitive tasks. Preclinical trials found that subjects on vortioxetine did better than those on duloxetine on the Digit Symbol Substitution Task (DSST), a measure of psychomotor speed (Gonzalez-Blanch C et al, *Arch Clin Neuropsychol* 2011;26(1):48–58). They then used the same outcome in 2 larger studies, each with 602 subjects. After 8 weeks, subjects on vortioxetine had higher scores on the DSST compared to those on placebo or those taking duloxetine, but by only 1.5%–3.0% (2 to 4 points on a 133-point scale) compared to placebo, and <0.5% (0.5 points) compared to duloxetine. On the strength of these studies, the company is applying for a new "cognitive dysfunction in MDD" indication. An FDA expert advisory panel recommended the approval in February, but just as we were sending this issue to press, the agency announced it would deny an expanded indication for cognitive dysfunction (http://www.biopharmadive.com/news/in-reversal-fda-denies-cognitive-dysfunction-label-expansion-for-brintelli/416536/).

We assume that the FDA's skepticism was related to a couple of important questions: First, do improvements on the DSST score translate into functional improvements that we (or our patients) would recognize clinically? Second, is vortioxetine any better than other antidepressants for improving cognition in depression?

In terms of the meaningfulness of its pro-cognitive properties, a recent meta-analysis found that while vortioxetine improves performance in the DSST, it didn't help patients on 3 other cognitive tests. These include the Stroop test (a measure of cognitive control), the Trail-Making Test B (executive function), and the Rey Auditory Verbal Learning Test (delayed recall) (Rosenblat JD et al, *Int J Neuropsychopharmacol* 2015;19(2).pii: pyv082.doi:10.1093/ijnp/pyv082). As a smart pill, vortioxetine's effects seem limited to one specific test—which doesn't improve our confidence in its efficacy.

Finally, are the cognitive benefits of vortioxetine—however modest they may be—a direct pro-cognitive effect? Or do they indirectly follow from vortioxetine's role as an antidepressant, thus implying that it won't perform better than any other treatment that eases depression? This question has not yet been fully answered, although one manufacturer-sponsored trial claims that the higher DSST scores were independent of its antidepressant effect (Mahableshwarkar AR et al, *Neuropsychopharm* 2015;40(8):2025–2037). Similar claims have also been made for duloxetine (Greer TL et al, *Dep Res Treat* 2014. Published online 2014 Jan 19. doi: 10.1155/2014/627863), but other antidepressants simply haven't been studied for their cognitive benefits.

TCPR Verdict: Will Brintellix make your patients "Brintellectuals"? The FDA is skeptical, and so are we.

Ketamine

Ketamine is not FDA approved for depression, but rather for preoperative general anesthesia. And it doesn't act on serotonin, norepinephrine, or dopamine; instead, it's an antagonist of the NMDA subtype of the glutamate receptor. It has long had illicit popularity in the party and rave scene under the nickname "special K." Of relevance to psychiatrists, ketamine has been touted as a potential fast-acting miracle antidepressant, and many clinicians are already offering it off-label to their patients in pop-up ketamine clinics. Should you jump on the ketamine bandwagon?

The ketamine antidepressant data

As of late 2015, nearly a dozen randomized clinical trials of intravenous ketamine for the treatment of depression had been published (DeWilde KE et al, *Ann NY Acad Sci* 2015;1345:47–58). These include some placebo-controlled trials, in addition to some open-label trials and a few trials with an active control (usually midazolam [Versed]). All showed, on average, a statistically significant response—defined as a 50% reduction in MADRS or Hamilton Rating Scale for Depression (HAM-D) symptom

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In Brief: Four Newer Antidepressants

Brand name	Ketalar	Brintellix	Fetzima	Viibryd
Generic name	ketamine	vortioxetine	levomilnacipran	vilazodone
Generic available?	Yes	No	No	No
Manufacturer	Multiple	Takeda / Lundbeck	Actavis	Actavis
Initial approval date	February 19, 1970	September 30, 2013	July 26, 2013	January 21, 2011
FDA indications	General anesthesia	Major depression	Major depression	Major depression
Dosages available	10, 50, 100 mg/ml (IV)	5, 10, 20 mg	20, 40, 80, 120 mg	10, 20, 40 mg
Dosing for depression	Not established	10–20 mg QD	40–120 mg QD	20–40 mg QD
Average cost	$500+ (per infusion)	$300 per month	$300 per month	$220 per month
Likely marketing points	Rapid response; efficacy for refractory patients	Cognitive improvement	Functional improvement; "norepinephrine depression" specific	Lack of sexual side effects; improvement in anxiety
Comments	Controlled substance: C III	FDA has denied approval of cognitive claims	No evidence of advantages over existing agents	Claims not yet substantiated

Research Updates IN PSYCHIATRY

DEPRESSION

Does Light Therapy Work for Non-Seasonal Depression?

(Lam R et al, *JAMA Psychiatry* 2016;73(1):56-63)

Many studies have shown that light therapy works for seasonal affective disorder, but does it work for non-seasonal major depression? That's less clear. Systematic reviews have yielded inconclusive results, in part because prior studies have had methodological weaknesses. A new study with a robust design was just published.

Over a 5-year period, researchers recruited 122 adult patients with non-seasonal major depression between the ages of 19 through 60 from three clinics in Canada. The patients were randomized to 1 of 4 groups: light therapy alone, fluoxetine 20 mg plus light therapy (combination treatment), fluoxetine 20 mg plus sham negative ion treatment, and double placebo (placebo pills plus negative ion). Light therapy was given with a 10,000-lux fluorescent light box for 30 minutes daily in the early morning. The study lasted 8 weeks, and 106 participants completed it. The primary outcome measure was change in the Montgomery-Åsberg Depression Rating Scale (MADRS); secondary outcomes included response and remission rates.

At study conclusion, both light therapy and combination therapy were superior to placebo; however, combination therapy beat placebo more consistently. Whereas light therapy yielded lower MADRS scores than placebo, combination therapy bested placebo on MADRS scores, response rates, and remission rates. Surprisingly, fluoxetine was not significantly better than placebo; the authors attribute this to small sample size.

Here are the numbers: Average improvements in MADRS scores were 16.9 (combined fluoxetine and light), 13.4 (light), 8.8 (fluoxetine and sham light), and 6.5 (placebo). Response rates (defined as ≥ 50% drop in MADRS score) for combined treatment, light, fluoxetine, and placebo were 76%, 50%, 29% and 33%, respectively. Remission rates (defined as MADRS score ≤ 10) were 59%, 44%, 19% and 30%.

TCPR's Take

This is probably the best designed clinical trial of light therapy for non-seasonal depression to date, and the results endorse both light monotherapy and combination light and fluoxetine, with the combination being possibly more robust. The bottom line is that, at least for depressed patients in the higher latitudes, you should consider recommending light therapy either alone or in combination with SSRIs.

—Bret A. Moore, Psy.D, ABPP

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

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scores—within 24 hours. Response rates have ranged from 40% to 70%. Some studies used only a single dose, with an antidepressant effect lasting up to 72 hours (even longer in some studies), while others involved repeated IV administrations over 2 weeks. The typical ketamine dose was 0.5 mg/kg given over a 40-minute period—as opposed to the anesthetic dose, which ranges from 1.0–4.5 mg/kg IV usually given over one minute.

Other studies have found that single infusions reduce suicidal ideation at 4 and 24 hours post-infusion (Price RB et al, *Biol Psychiatry* 2009;66:522–526). Investigators are now trying to identify subgroups who are more likely to respond to ketamine. There aren't enough data yet to predict response, but some potential positive indicators include a family history of alcoholism, comorbid anxiety, or an elevated body mass index (Niciu MJ et al, *J Clin Psychiatry* 2014;75:e417–423).

Ketamine in the office?

So if it provides such rapid relief to some people who have been refractory to other treatments, why hasn't ketamine caught on? One major hurdle, of course, is the fact that it's an intravenous medication, making it much more complicated to prescribe than a pill. Because of potential, though rare, side effects such as an acute hypertensive crisis, the IV infusion should take place in a medical office equipped with vital sign monitoring, airway equipment, oxygen, and a crash cart. Some even advise the presence of a trained anesthesiologist (Sisti D et al, *Curr Psychiatry Rep* 2014;16:527). These requirements likely explain the high out-of-pocket costs (up to $500–$750 per infusion) for this off-label procedure at the handful of ketamine clinics that have popped up nationwide over the last few years. Other potential adverse effects, like an uncomfortable dissociative experience, as well as long-term cognitive impairment and the risk of diversion or recreational abuse of ketamine, must be considered.

Furthermore, no one really knows how long to provide the treatment. In the 2-week trials described above, which involved 6 infusions, relapse rates were as high as 55% to 89% in the month following treatment (Newport DJ et al, *Am J Psychiatry* 2015;172:950–966). No "maintenance" strategy has been described, and no other medications have been shown to extend ketamine's antidepressant effect.

Finally, it's still not clear that the standard 0.5 mg/kg intravenous dose is the "best" dose. This dose was chosen, in part, because it produces few side effects; these are typically transient dissociative symptoms ("I feel like I'm floating") or hallucinations during the infusion. While these effects are short-lived, they have also been positively associated with a treatment response (Luckenbaugh DA et al, *J Affect Disord* 2014;159:56–61). Thus, dissociative effects may predict—or may even be responsible for—the antidepressant effect. If this is true, it may be hard to find a dose that minimizes unpleasant psychoactive effects while also producing a robust antidepressant effect. Then again, some practitioners are deliberately using higher doses of ketamine,

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CME Post-Test

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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 are listed on page 1.

1. Which of the following drugs is an antagonist of the NMDA subtype of the glutamate receptor? (Learning Objective #2)
   [ ] a. vilazodone [ ] b. levomilnacipran [ ] c. vortioxetine [ ] d. ketamine

2. According to the STAR*D trial, treatment for major depression with an SSRI brings about remission in what percentage of depressed patients? (LO #1)
   [ ] a. 15% [ ] b. 28% [ ] c. 49% [ ] d. 60%

3. A recent meta-analysis found that vortioxetine improved performance in which cognitive test? (LO #2)
   [ ] a. The Digit Symbol Substitution Task [ ] b. The Stroop test
   [ ] c. The Trail-Making Test B [ ] d. The Rey Auditory Verbal Learning Test

4. Which of the following symptoms does SSRI treatment most effectively treat? (LO #1)
   [ ] a. Anergia [ ] b. Apathy [ ] c. Insomnia [ ] d. Anxiety

5. True or false: A recent study's findings on light therapy for non-seasonal depression implies that it doesn't have an effect on depressed patients. (LO #3)
   [ ] a. True [ ] b. False

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Expert Interview
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they can develop Type 2 diabetes and experience other problems, so these drugs should not be prescribed without caution. But used appropriately they are often a sensible component of treatment.

TCPR: What about patients who may be in need of a more stimulant-like medicine?

Dr. Bodkin: You can always try psychostimulants like amphetamine or methylphenidate, but doctors are often uncomfortable prescribing them, and patients can be uncomfortable receiving them. There are some alternatives. For patients whose depression is characterized by lethargy, apathy, dragging of the feet, etc. there is the partial agonist strategy of aripiprazole (Abilify) or brexpiprazole (Rexulti). In addition, sometimes pramipexole (Mirapex) is remarkably helpful if you have a patient who ideally should have been started on an MAOI but instead is taking an SNRI and is still lethargic. Pramipexole is a direct dopamine agonist used for Parkinson's and for restless leg syndrome. It's sort of a stimulant-like drug without the stimulant-like problems of potential abuse and tolerance.

TCPR: What sort of side effects should I be warning my patient about when I'm using pramipexole?

Dr. Bodkin: Both hypotension and nausea are potential problems, and sometimes people paradoxically get quite sedated. In older patients, especially those who have some degree of dementia, there can be a side effect of impulsivity or excessive initiative. It's also inconvenient. It's a t.i.d. drug, occasionally a b.i.d. drug, so dosage has to be titrated with great care.

TCPR: So there are a lot of options out there. It can get confusing. Can you help us with our decision-making?

Dr. Bodkin: I often look at symptoms in terms of a very simple bifurcation: the distress factor vs. the drive factor (Watson D and Tellegen AJ, *Pers and Soc Psychol* 1988;54(6):1063–1070). The distress factor has to do with anxiety, irritability, rage, panic, etc. These symptoms call for anxiolytic medications—SSRIs, benzodiazepines, many of the atypical antipsychotics. The drive factor has to do with initiative, interest, and energy level. If there is too much of those, we call it hypomania, but patients need at least an average amount of initiative, interest, and gratification from the pursuit of things that are interesting. Diminished drive leads me to reach for dopaminergic interventions, and to a lesser extent to noradrenergic interventions. As we discussed, these include stimulants, bupropion, aripiprazole, pramipexole, but also MAOIs, which among other things inhibit metabolism of dopamine.

TCPR: That is very interesting. Thank you for your time, Dr. Bodkin.

THE CARLAT REPORT: PSYCHIATRY

P.O. Box 626
Newburyport, MA 01950

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This Month's Focus:
Antidepressant Roundup

Next month in *The Carlat Psychiatry Report:* Correctional Psychiatry

Four Newer Antidepressants: Should You Use Them?

Continued from page 6

sometimes in intramuscular or oral forms, in order to induce a psychedelic state, which they see as a necessary component of healing (Dakwar E et al, *Drug Alc Depend* 2014;136:153–157).

Pharmaceutical companies have eagerly embraced the ketamine story, in hopes of developing a similar drug without ketamine's reputation and its pesky DEA Schedule III designation. But the options are limited. AstraZeneca tested one compound, lanicemine, but quietly backed out after it failed a Phase IIb trial in 2015. Another compound called GLYX-13 (recently renamed rapastinel), a partial agonist at another site on the NMDA receptor, has been effective in reducing HAM-D scores relative to placebo at some doses, and further research is ongoing. Other labs are studying the tuberculosis drug D-cycloserine, another NMDA modulator, as well as other agents. The closest thing to ketamine in the commercial pipeline is Janssen's intranasal S-ketamine (an enantiomer of ketamine), currently in phase II trials.

Of course, if you want to explore this territory on your own, IV ketamine is readily available. It can be compounded into oral, sublingual, and intranasal forms. But its use in depression remains strictly off-label and, at this time, must be seen as experimental. As more data become available and protocols are published and refined, it may be worth your time and effort to add it to your repertoire.

TCPR Verdict: Ketamine looks promising for extremely rapid relief of depression—but the effects are short-lived, and any antidepressant that requires a crash cart nearby is not likely to become a blockbuster.