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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Bipolar Disorder

Learning Objectives

After reading these articles, you should be able to:

1. Assess the use of lithium and antidepressants in the treatment of bipolar disorder.
2. Identify the limitations and efficacy of various treatments in depression.
3. Understand the role of orexin antagonists for insomnia.
4. Summarize some of the current research findings on psychiatric treatment.

Six Recent Disappointments in Psychiatric Research

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

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

Our articles often focus on treatments that work, but it's worth pausing to review the recent disappointments. They include an industry-sponsored trial of cariprazine (Vraylar) in major depression, a condition for which it has FDA approval as an augmentation to antidepressants.

Cariprazine

Cariprazine (Vraylar) is FDA approved for augmentation of antidepressants in major depressive disorder, but a new study casts doubt on its efficacy there. This industry-sponsored trial randomized 750 patients to receive cariprazine 1.5 mg, cariprazine 3 mg, or placebo as augmentation to their antidepressant. After six weeks, cariprazine failed to separate from placebo, although nonsignificant trends were seen in the higher 3 mg dose. The authors blamed the

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Highlights From This Issue

Q&A. Antipsychotics work faster in bipolar mania, but Dr. Michael Gitlin finds something in lithium that patients appreciate more over the long term.

Article on page 5. Orexin antagonists have unique advantages in sleep: less addiction, better safety in the elderly, and improved daytime functioning.

Research update on page 6. PEA, a natural peanut extract, gained preliminary support as antimanic augmentation in bipolar disorder.

Q&A With the Expert

Lithium, Antidepressants, and Bipolar Disorder
Michael J. Gitlin, MD

Professor of Clinical Psychiatry and Director of the Mood Disorders Clinic at the David Geffen School of Medicine at UCLA; coauthor of The Essential Guide to Lithium Treatment *(Springer, 2016).*

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

TCPR: What are we getting wrong in the way we treat bipolar disorder?

Dr. Gitlin: There's been a marked decline in the use of lithium over the past 20–30 years. There are reasons not to use it, and certainly the need for lab monitoring is not trivial, but lithium is arguably the gold-standard drug, so we ought to rethink this trend. Lithium is not first line for everybody, but something is wrong when so many patients with bipolar disorder have tried multiple anticonvulsants and antipsychotics without ever having a chance on lithium. The other problem is antidepressants. There's a disparity between what bipolar experts think and what clinicians do here. Most guidelines say, "Don't use antidepressants first line," but in practice they are used much more liberally.

TCPR: What is your view on antidepressants in bipolar?

Dr. Gitlin: My personal view is that antidepressants

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failure on a high placebo response rate, but equal responsibility falls on the drug itself, which yielded only a small effect size (0.3) in previous trials (Riesenberg R et al, *J Clin Psychiatry* 2023;84(5):22m14643).

Cariprazine is also FDA approved in bipolar depression, and its track record is uneven there as well. It failed in unpublished trials of bipolar II depression and had only a small effect in bipolar I depression. In contrast, both lumateperone and quetiapine proved effective in bipolar I and II depression.

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Esketamine

Esketamine (Spravato) also posted a recent failure in a disorder where it is FDA approved: treatment-resistant depression. Esketamine showed early promise in this industry-sponsored trial of 252 patients, separating from placebo within 24 hours. Those benefits quickly subsided, however, and were no longer detectable by week four. This pattern is not out of character for esketamine. In its positive trials, it brought about rapid improvements that lessened over the first four weeks. Like cariprazine, its overall effect size in major depression is small (0.3) (Chen X et al, *Neuropsychiatr Dis Treat* 2023;19:693–707).

Zuranolone

Zuranolone is a GABAergic steroid that has been newly approved as Zurzuvae in postpartum depression. Its trials were consistently positive in that disorder, but it missed the mark in major depressive disorder. Like esketamine, zuranolone brought rapid improvement in major depression, but its benefits fizzled out within one to two weeks in several large trials. This is not surprising for a medication that resembles a benzodiazepine in both its mechanism and its rewarding qualities (see the January 2024 issue of *The Carlat Psychiatry Report* for reference).

Minocycline, simvastatin, and pimavanserin

The antibiotic minocycline, the statin simvastatin, and the novel antipsychotic pimavanserin (Nuplazid) brought unique mechanisms to depression. Although earlier, small studies were positive, each failed this year in well-designed randomized trials. Their failure on the larger stage may end these pursuits, although minocycline still has hope (Hellmann-Regen J et al, *JAMA Netw Open* 2022;5(9):e2230367; Husain MI et al, *JAMA Netw Open* 2023;6(2):e230147; Dirks B et al, *Psychopharmacol Bull* 2022;52(4):8–30).

Minocycline has enough positive trials in major depression to gain an endorsement from a 2023 meta-analysis (Qiu Y et al, *Front Psychiatry* 2023;14:1139273). Its mechanism is complex, involving neuroprotective, anti-inflammatory, glutamatergic, and monoaminergic activities. In one study, it worked preferentially in depressed patients with high levels of inflammation (as measured by a high-sensitivity CRP ≥3). The typical dose is 200 mg daily.

N-acetylcysteine (NAC)

NAC is the main antioxidant in the brain. It has been tested in various conditions over the past 20 years, but it has never had a straight record of success. Encouraging results in trichotillomania, depression, OCD, negative symptoms of schizophrenia, and cannabis use disorder have all been countered by negative studies of a similar size and design. At best, NAC works in bipolar but not unipolar depression, and it has a slow build. In the positive bipolar trial at a dose of 2,000 mg/day, it took four to six months to see an effect (Berk M et al, *Biol Psychiatry* 2008;64:468–475).

NAC may have a role in psychiatric symptoms that occur during a substance use disorder. Recently, it improved depression and anxiety in a small, placebo-controlled trial of opioid use disorder (Padoei F et al, *Brain Behav* 2023;13(1):e2823). Although it failed in a recent trial of treatment-resistant PTSD, it did work in an earlier PTSD trial that enrolled patients with comorbid addictions (Kanaan RA et al, *Psychiatry Res* 2023;327:115398).

On the other hand, NAC's ability to directly reduce substance use looks less promising. Earlier, it failed in cocaine use disorder, and this year it failed in two small randomized controlled trials of alcohol use disorder (Morley KC et al, *Alcohol Alcohol* 2023;agad044; Kirkland AE et al, *Neuropsychopharmacology* 2023;48(8):1184–1193).

The MIND diet

The MIND diet, a Mediterranean-style approach to prevent dementia, gained popularity quickly when it was developed in 2015. It had robust support from basic science and epidemiologic studies, and a panel of *US News*–appointed experts

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ranked it the second best diet for overall health.

The MIND diet failed this year in its first randomized trial, a well-designed, three-year study that looked at cognitive outcomes on the diet compared to a control diet in 604 people. The participants entered the study with normal cognition but had characteristics that would predict a good response to the diet. They were older (average age 70), were overweight, ate a poor diet, and had a family history of dementia. Yet they had no benefit on objective measures of cognition or brain MRIs (Barnes LL et al, *N Engl J Med* 2023;389(7):602–611).

Those who purchased one of the two dozen MIND diet cookbooks can still find use for this approach. A similar diet treated major depressive disorder with a large effect size in three controlled trials, and improved childhood ADHD in another (see the November/December 2021 and October/November 2022 issues of *The Carlat Psychiatry Report*). Like the MIND diet, the nutritional plans in these studies were based on the heart-healthy Mediterranean and DASH diets. The difference? The MIND diet sets a stricter limit on cheese, based on a theory that diacetyl from cheese contributes to the amyloid plaques that are implicated in dementia.

CARLAT VERDICT

It's just as important to pay attention to negative results as to positive results. For the medications I've discussed in this article, we now believe the following:

- On average, we can expect weak effects from cariprazine in depression.
- Esketamine's antidepressant benefits decline after a few weeks.
- Zuranolone is effective for postpartum depression but not for standard major depression.
- Simvastatin and pimavanserin appear ineffective in depression.
- The picture is not yet clear for NAC and minocycline, which may have a role in certain types of depression.

Expert Interview

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have been given a much worse rap than they deserve. There are now sufficient data showing that antidepressants can be used safely as monotherapy in patients with bipolar II disorders—and in bipolar I disorder if the patient is on a mood stabilizer (Cheniaux E et al, *Exp Opin Drug Safety* 2019;8(10):893–913). But they should not be used in bipolar I as monotherapy, and they are not first line in bipolar II depression. We have other options like lamotrigine, lithium, lumateperone, lurasidone, and quetiapine for bipolar depression.

TCPR: What are the risks with antidepressants?

Dr. Gitlin: The risks are mood switching to mania, mixed states, or hypomania, and—over the long term—rapid cycling. The consequences are greater in patients with bipolar I, who are much more likely to switch all the way into the more destructive state of mania. In bipolar II, we see more switches into hypomania, and the overall switch rate is about half for bipolar II versus bipolar I. In bipolar I disorder, half the switches are into mania and half are into hypomania, whereas in bipolar II, 90% of the switches are into hypomania—which is, by definition, a much less destructive state.

TCPR: Do you have a preferred antidepressant in bipolar disorder?

Dr. Gitlin: This varies a lot by patient. In the research, bupropion and SSRIs have the lowest switch rates, and then venlafaxine and—for the highest switch rates—the tricyclics. Studies of MAOIs are few, but their risk appears somewhere between that of the SSRIs and the tricyclics. But there are many antidepressants where we don't have reliable information on the switch rates: mirtazapine, trazodone, selegiline (an MAOI Emsam patch), and the other SNRIs besides venlafaxine (Barbuti M et al, *Eur Neuropsychopharmacol* 2023;73:1–15).

TCPR: You mentioned that lithium use is on the decline. That trend has accelerated with the approval of antipsychotics in bipolar disorder.

Dr. Gitlin: Yes, the first atypical to gain approval in acute mania was olanzapine in 2000, but antipsychotics were used for mania long before that. In the 1960s, it was lithium versus chlorpromazine (Thorazine), and when I read those papers, I realized you could have substituted the word olanzapine for chlorpromazine and everything they found would still be correct. Things have not changed much.

TCPR: What are the meaningful differences between lithium and antipsychotics in bipolar disorder?

Dr. Gitlin: Antipsychotics work faster and are better at controlling behavioral agitation. Lithium is slower, but it has more of a normalizing feeling to patients (Bergamelli E et al, *CNS Drugs* 2021;35(11):1275–1287). Lithium is not sedating the way chlorpromazine and olanzapine are, so patients don't feel like they "have a blanket over their head" when on lithium. But it often takes more than a few weeks to recover from mania on lithium, and it's not as good at controlling the agitation or insomnia.

TCPR: That may explain why antipsychotics are preferred on inpatient units. They lead to faster improvement.

Dr. Gitlin: Yes, and some of that is due to their sedating effects. For the nursing team—or the family if the patient is at home—calming the agitation is an important goal. Sometimes patients want that too, but not over the long term, and sedation is not actually necessary for recovery from mania. Less sedating antipsychotics like risperidone and aripiprazole work just as well as sedating ones like olanzapine. Another strategy is to use a benzo along with a nonsedating antipsychotic or mood stabilizer, and then taper the benzo off as the mania improves.

TCPR: Is there a preferred benzo in bipolar disorder?

Dr. Gitlin: There are no clinical data suggesting one is clearly better than another, but in practice, I prefer clonazepam for pragmatic reasons: It only has to be dosed once or twice a day.

TCPR: So antipsychotics work faster in mania, but how do you know what will work best over the long term?

Dr. Gitlin: We know the most about who does well on lithium long term. About 20% of people with

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bipolar disorder have a lightbulb response to lithium, and the more they fit the textbook case of bipolar disorder, the more likely they are to respond to it. That means they have discrete episodes of classic-looking mania and depression that are separated by clear periods of normal "euthymic" mood. They lack mixed features and rapid cycling. Another predictor is that the depressions tend to come on after the manias in a mania-depression-well interval (MDI) pattern, as opposed to the opposite: depression-mania-well interval (DMI) (Hui TP et al, *Acta Psychiatr Scand* 2019;140(2):94–115).

TCPR: What about comorbidities?

Dr. Gitlin: Some say that comorbidities like anxiety or substance use disorders predict a poorer response to lithium, but I think they just predict a poorer response to almost anything. There is evidence, though, that valproic acid (Depakote) has a favorable response for those with comorbid alcohol use disorders (Le Fauve CE, *Evid Based Ment Health* 2005;8(3):79).

TCPR: What works better for patients with mixed features?

Dr. Gitlin: The antipsychotics and anticonvulsants, of which valproate is the anticonvulsant with the most research in mixed features. In rapid cycling, though, it is not as clear. We used to think lithium was less effective in rapid cycling, but Joe Calabrese did a large, 20-month, randomized comparison of lithium and valproate and found that both had similar outcomes and neither worked particularly well (Calabrese JR et al, *Am J Psychiatry* 2005;162(11):2152–2161). It looks like rapid cycling is a bad patch of the illness that nothing works well in, but the good news is that this is temporary. Most cases resolve within the first few years, so rapid cycling doesn't define the individual.

> **"Sedation is not actually necessary for recovery from mania."**
>
> Michael J. Gitlin, MD

TCPR: Do you know of any other markers for antipsychotic or anticonvulsant response?

Dr. Gitlin: No, we don't have any good data. We tend to use lamotrigine when depressions predominate in bipolar disorder, as they often do in bipolar II.

TCPR: What have we learned about lithium in recent years?

Dr. Gitlin: It looks like we've been targeting blood levels that were higher than necessary. For maintenance treatment, the target is now 0.6–0.8 mEq/L, but it used to be thought of as 0.8–1.0 mEq/L (Nolen WA et al, *Bipolar Disord* 2019;21(5):394–409). Lower levels mean higher adherence and fewer side effects. Another exciting finding is that lithium is neuroprotective, which is ironic considering many patients complain of cognitive dulling on it. That side effect usually improves by lowering the dose, but over the long term, lithium may prevent dementia (see *The Carlat Psychiatry Report*, September 2022). Lithium also protects the ends of DNA—the telomeres—which are involved in cellular death and aging.

TCPR: Any new risks with lithium?

Dr. Gitlin: This is not a new side effect, but there is greater awareness of hyperparathyroidism on lithium, which can lead to osteoporosis and renal stones if not corrected. Most patients are asymptomatic, or may complain of fatigue or cognitive fuzziness, so you have to detect it through labs. At a minimum, that means monitoring calcium on routine lithium labs, and if it is elevated, I'd check the parathyroid hormone (PTH) and refer to endocrinology. Another update is not a risk, but there's been some controversy around lithium's ability to prevent suicide. A lot of studies suggest lithium prevents suicide, and not just because it's a good mood stabilizer—we see this effect in unipolar mood disorders as well, and it is partly independent of lithium's mood benefits (Smith KA and Cipriani A, *Bipolar Disord* 2017;19(7):575–586).

TCPR: What called that into question?

Dr. Gitlin: A VA trial randomized patients with mostly unipolar mood disorders to lithium or placebo, but it was halted for futility after researchers found no difference in the first 519 patients they enrolled, even though one in four of them had suicide-related events (Katz IR et al, *JAMA Psychiatry* 2022;79(1):24–32). But there were problems with this study—for example, only half of the sample had lithium levels above 0.5 mEq/L.

TCPR: Are there any medical complications that would make you stop lithium?

Dr. Gitlin: That always has to be balanced with the psychiatric risks. Even with renal disease, like when the eGFR (estimated glomerular filtration rate) goes below 60 mL/min—which is the general cutoff for chronic kidney disease—we may have to keep the patient on lithium. Sure, you'd want to consider other options and get the lithium level as low as possible, but if the alternative is frequent mania, hospitalizations, or suicide, they may need to stay on it (Salgado ME et al, *Int J Bipolar Disord* 2014;2(1):12).

TCPR: Is long-term prevention with a mood stabilizer always necessary in bipolar disorder?

Dr. Gitlin: For bipolar I, the answer is generally yes. For bipolar II, the risk/benefit ratio is different because—although recurrence of mood episodes is high—patients are not going to have the kinds of manias that can destroy their lives. Some practice guidelines outside the US say you can consider taking patients with bipolar I off a mood stabilizer after just one manic episode as long as it wasn't severe—like floridly psychotic or requiring hospitalization. But the relapse rates are very high, so I recommend long-term prevention even after one manic episode. The problem is that the first episode usually occurs in the teenage or early adult years when people have an inflated feeling of being in control of their lives. They think that the first episode was due to a life event, and they often won't agree to long-term treatment until the second or third episode.

TCPR: Are psychiatrists overdiagnosing or underdiagnosing bipolar disorder?

Dr. Gitlin: For bipolar I patients, we do a reasonably good job. Nobody is going to miss florid mania, although we may not pick up on it if it's buried in the patient's history and we don't get old records or speak to the family. Bipolar II is easier to miss because hypomania can be a very subtle state and can be positive—and not feel like psychopathology.

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New Medications for Insomnia

Garrett Rossi, MD. Inpatient/Consult Attending Psychiatrist, AtlantiCare Regional Medical Center, Pomona, NJ.

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

Much of what we do in psychiatry involves helping patients get to sleep, whether they are experiencing depression, anxiety, mania, or just primary insomnia. Over the last several years, we've seen the introduction of sleep medications that block orexin receptors. These medications are considered safer than the hypnotics and sedating antidepressants used in the past, but they come with some challenges of their own in practice. In this article, I will review when and how to use the dual orexin receptor antagonist medications (DORAs): daridorexant (Quviviq), lemborexant (Dayvigo), and suvorexant (Belsomra).

How do orexin antagonists work?

Orexin neurons are located primarily in the hypothalamus, an area of the brain known as the "control center" because it regulates the homeostatic balance of many bodily functions, including sleep. High concentrations of orexin receptors in the monoamine centers located in the brainstem are often thought of as "wake-promoting," but their real function may be to mediate wakefulness by regulating arousal and promoting neurotransmitters such as acetylcholine, dopamine, histamine, norepinephrine, and serotonin. There are two types of orexin receptors—orexin 1 and 2—and the orexin antagonists induce sleep by blocking both receptors.

In narcolepsy, the orexin neurons degenerate, causing sudden sleep attacks throughout the day. Using an orexin antagonist in narcolepsy is absolutely contraindicated because it would cause cataplexy in this population (Muehlan C, *J Sleep Res* 2023;32(6):e13902).

How well do orexin antagonists work?

Like the Z-hypnotics, orexin antagonists are only FDA approved for primary insomnia. In randomized controlled trials (RCTs), orexin antagonists reduced time to sleep onset, reduced nocturnal awakenings, and increased total sleep time.

Two pivotal randomized placebo-controlled trials resulted in FDA approval for suvorexant. It outperformed placebo on all subjective as well as polysomnography end points in the first week of treatment, at one month, and at three months. Suvorexant was well tolerated, with fewer than 5% of patients discontinuing treatment due to adverse events, and there were no signs of withdrawal symptoms or rebound insomnia when discontinued (Herring WJ et al, *Biol Psychiatry* 2016;79(2):136–148). Lemborexant shared similar success in a multicenter RCT that showed a decrease from baseline in patient-reported sleep onset, a decrease in waking after sleep onset, and an increase in sleep efficiency, in all cases significantly outperforming placebo (Kärppä M et al, *Sleep* 2020;43(9):szaa123).

The newest DORA is daridorexant, which has a shorter half-life at eight hours, compared to 17–19 hours for lemborexant and 15 hours for suvorexant. In a multicenter RCT, a dose-dependent improvement in reducing waking after sleep onset and sleep latency was observed compared to placebo. Doses of 25 mg and 50 mg improved sleep outcomes, but the 50 mg dose also improved daytime functioning in people with insomnia (Mignot E et al, *Lancet Neurol* 2022;21(2):125–139). Suvorexant and lemborexant brought similar improvements in daytime functioning.

Although these medications have not been compared head-to-head, lemborexant and suvorexant were indirectly compared in a network meta-analysis. Lemborexant 10 mg had the largest effect size compared to placebo for all primary outcomes, but it had a higher risk of daytime somnolence (Kishi T et al, *Psychiatr Res* 2020;128:68–74). Despite that risk, the two drugs had similar rates of discontinuation due to adverse effects.

One advantage of the DORAs is their safety record in the elderly population (65 years and older). No new problems stood out in the trials that focused on the elderly, even when the patients were woken in the middle of the night to assess their balance. The DORAs also have a low risk of causing next-day memory problems. Among the hypnotics, only ramelteon has a similar safety profile in the elderly. Trazodone has a reputation as a safe hypnotic, but it carries cardiac risks and can cause falls by causing orthostatic hypotension (Murphy P et al, *Clin Sleep Med* 2020;16(5):765–773).

In the United States, all DORAs are scheduled in the same class as Z-hypnotics (Schedule IV), indicating a low risk of abuse and dependence. Animal studies found no evidence of withdrawal and a low risk of reinforcing effects (Born S et al, *Regul Toxicol Pharmacol* 2017;86:181–192; Schoedel KA et al, *J Clin Psychopharmacol* 2016;36(4):314–323; Landry I et al, *J Clin Psychopharmacol* 2022;42(4):365–373). However, studies that tested high doses of DORAs in people with a history of recreational sedative use did find a potential for misuse (Ufer M et al, *Sleep* 2022;45(3):zsab224). If misuse

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Summary of FDA-Approved DORA Medications

Dual Orexin Receptor Antagonist (DORA)	FDA Approval for Insomnia	Doses	Onset	Half-Life	Metabolism	Monthly Cost
Daridorexant (Quviviq)	2022	25 mg, 50 mg	<30 min	8 hours	CYP3A4	$500
Lemborexant (Dayvigo)	2019	5 mg, 10 mg	<30 min	5 mg: 17 hours 10 mg: 19 hours	CYP3A4/5	$300
Suvorexant (Belsomra)	2014	5 mg, 10 mg, 15 mg, 20 mg	30 min	15 hours	CYP3A4 (major) CYP2C19 (minor)	$425

Research Updates IN PSYCHIATRY

BIPOLAR DISORDER

PEA: A Natural Anti-Inflammatory for Mania?

Kate Travis, MD. Dr. Travis has no financial relationships with companies related to this material.

REVIEW OF: Abedini T et al, *Psychiatry Clin Neurosci* 2022;76(10):505–511

STUDY TYPE: Randomized, double-blind, placebo-controlled trial

Palmitoylethanolamide (PEA) is a naturally occurring fatty acid amide found in foods like peanuts and eggs. It has anti-inflammatory, neuroprotective, and analgesic effects. PEA successfully augmented antidepressants in a small, controlled trial of major depression (Hashemi et al, *J Affect Disord* 2018;232:127–133), and the current study explored its potential in bipolar mania.

Researchers conducted a six-week, randomized, double-blind, placebo-controlled study of PEA as an adjunctive treatment for mania. They enrolled 63 adult patients who were admitted for bipolar mania at two hospitals in Iran. All patients were taking combined lithium (0.8–1.1 mEq/L) with risperidone (3 mg), and half additionally received a PEA tablet (600 mg) while the other half got a placebo pill. Manic symptoms were assessed at baseline and weeks one, two, four, and six by the Young Mania Rating Scale (YMRS). The primary outcome was reduction of YMRS scores from baseline to study endpoint between the PEA and placebo groups.

Patients in the PEA and placebo groups started with statistically similar YMRS scores (31.34 and 29.96, respectively), indicating moderate mania. Those randomized to adjunctive PEA had a significant reduction in YMRS scores compared to placebo at four weeks (-22.46 vs -18.00, p=0.018) and six weeks (-29.06 vs -23.22, p=0.002). Both groups had low YMRS scores at the end of the six-week trial, though scores were significantly lower in the PEA group (2.28 vs 6.74, p=0.004). PEA was well tolerated, with no difference in adverse events between the PEA and placebo groups.

CARLAT TAKE

This study adds to a small but growing body of literature suggesting that anti-inflammatory agents like PEA may be effective adjunctive treatments for acute mania, but we'll need more than a single study before recommending PEA in practice.

DEPRESSION

Cognitive Training Extends Ketamine's Benefits

Avneet Soin, MD. Dr. Soin has no financial relationships with companies related to this material.

REVIEW OF: Price RB et al, *Am J Psychiatry* 2022;179(12):959–968

STUDY TYPE: Randomized, double-blind, parallel-arm trial

Ketamine can bring rapid relief in difficult-to-treat depression, but its benefits are unfortunately short-lived. Many medications have been tested, but none have helped patients stay well after ketamine treatment. So far, the only known intervention that prolonged ketamine's antidepressant effects in a controlled trial was cognitive behavioral therapy. In the current study, researchers tested whether a different psychological intervention could prolong ketamine's benefits.

The intervention, automated self-association training (ASAT), is a computerized system that pairs positive phrases (such as "sweet") with self-referential stimuli (such as photos of the patient). The positive phrases are delivered both as rapid, subliminal messages on the screen as well as at a level of conscious perception. The device is under patent, and one of the study authors is the inventor. Patients viewed ASAT for 15–20 minutes a day over four days following ketamine infusion. A sham version of ASAT, which paired neutral traits with non-self-referential stimuli, was used as the placebo control.

This double-blind, parallel-arm study randomized 154 patients with major depression into three arms: ketamine/ASAT, saline/ASAT, and ketamine/sham ASAT. All patients had failed at least one antidepressant trial. The mean age was 34, and most subjects were White (75%) and female (63%). The primary outcome was severity of depression trended by the Montgomery-Åsberg Depression Rating Scale over 30 days.

Compared to the sham intervention, the group that received ketamine with ASAT stayed well longer. Over the 30-day follow-up period, depression scores increased gradually in the sham group but remained more stable and lower in the ASAT group. This difference was not detectable at 24 hours post-infusion, at which point the two ketamine-treated arms experienced similar improvements, and both ketamine arms were superior to the saline infusion arm.

While these findings were statistically significant, the 30-day effect size was small when looking at ketamine/ASAT compared to ketamine/sham (β = -0.31, 95% confidence interval [CI] = -0.75, 0.13), as well as for ketamine/ASAT compared to saline/ASAT (β = –0.38, 95% CI = -0.78, 0.027).

CARLAT TAKE

Ketamine's long-term effects may depend on the psychological context in which it is delivered. While the psychological intervention tested here is not readily available, the results open the door to explorations of ketamine-assisted psychotherapy.

CME Post-Test

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1. Which statement about the use of lithium for bipolar disorder is accurate (LO #1)?
   - [ ] a. Lithium is more effective for rapid-cycling bipolar disorder
   - [ ] b. The target blood level for maintenance treatment with lithium is 1.0–1.2 mEq/L
   - [ ] c. Lithium is associated with a risk of hyperparathyroidism
   - [ ] d. The use of lithium has increased over the past 20–30 years

2. What was the outcome of an industry-sponsored trial from 2023 that investigated cariprazine (Vraylar) as an augmentation to antidepressants in major depressive disorder (LO #2)?
   - [ ] a. Cariprazine demonstrated significant efficacy compared to placebo
   - [ ] b. Cariprazine showed a nonsignificant trend toward efficacy with the 1.5 mg dose
   - [ ] c. The trial established the superiority of cariprazine over lumateperone and quetiapine
   - [ ] d. The study attributed the failure of cariprazine to a low placebo response rate

3. What is the primary mechanism of action of DORAs in the treatment of insomnia (LO #3)?
   - [ ] a. Enhancing acetylcholine and dopamine release in the brain
   - [ ] b. Blocking orexin receptors in the hypothalamus
   - [ ] c. Increasing orexin production in the hypothalamus
   - [ ] d. Inhibiting serotonin reuptake in the brain

4. Which natural therapy showed efficacy in a recent controlled trial as augmentation in bipolar mania (LO #4)?
   - [ ] a. Inositol
   - [ ] b. Omega-3 fatty acids
   - [ ] c. Palmitoylethanolamide (PEA)
   - [ ] d. Melatonin

5. What is Dr. Gitlin's perspective on the use of antidepressants in bipolar disorder (LO #1)?
   - [ ] a. Antidepressants are recommended as monotherapy for bipolar I depression
   - [ ] b. Antidepressants are recommended, but are not first line, in bipolar II depression
   - [ ] c. Antidepressants are the preferred treatment for bipolar depression
   - [ ] d. Antidepressants are not recommended for any type of bipolar depression

New Medications for Insomnia

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is a concern, a nonscheduled hypnotic like doxepin or ramelteon is a good alternative.

Adverse effects

The most common adverse effects are dose related and include daytime somnolence and fatigue. Like other hypnotics, the DORAs carry a warning about complex sleep behaviors (eg, sleepwalking, sleep driving), sleep paralysis, hypnagogic/hypnopompic hallucinations, and worsening depression or suicidal ideation. These risks are more strongly associated with the benzodiazepines and Z-hypnotics than the DORAs, but their possibility cannot be ruled out (McCall WV et al, *Am J Psychiatry* 2017;174(1):18–25). Narcolepsy is the main contraindication to their use.

How to use orexin antagonists

With their safety advantages over the Z-hypnotics and benzodiazepines, the DORAs could be used first line for insomnia, were it not for their cost. Many insurers will require a documented failure of alternative hypnotics before approving them.

The directions for DORAs are similar to other hypnotics: Get into bed after taking the medication and allow for seven hours of sleep before rising. The DORAs begin to take effect within 30 minutes, and that effect is delayed if taken with a large or fatty meal. Daridorexant has the shortest half-life at eight hours, compared to 17–19 hours for lemborexant and 15 hours for suvorexant. All three medications are primarily metabolized by CYP3A4.

Data for transitioning from benzodiazepines or Z-hypnotics are limited, but a small RCT did find that switching from a benzo to suvorexant was effective in patients whose insomnia was unresponsive to long-term benzodiazepine therapy (Shigetsura Y et al, *Clin Neuropharmacol* 2022;45(3):52–60). Whether to cross-taper from a benzo or Z-hypnotic is less clear. On the one hand, withdrawal effects may obscure any benefits from the new hypnotic. On the other hand, one study found a significant increase in sedation when suvorexant was added to existing benzodiazepine treatment (Hatano M et al, *Clin Psychopharmacol Neurosci* 2018;16(2):184–189).

CARLAT VERDICT

DORAs fill a much-needed gap in insomnia research. They offer an enhanced safety profile with decreased risk for withdrawal and dependence, but cost and lack of evidence in psychiatric disorders other than primary insomnia remain barriers to widespread clinical use.

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PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

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Expert Interview
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That's where a close friend or relative's observations are critical. If I'm wondering whether we're dealing with hypomania or another form of affective lability like borderline personality disorder, I will ask to speak with someone who knows the patient well. First, I reassure the patient that I'm not going to reveal any information and invite them to be there while we talk. I find outside observers are critical for two diagnoses: bipolar II and ADHD. Yes, it's critical, but what really confirms the diagnosis is long-term observation.

TCPR: How long do you need before you're fairly confident in the diagnosis?

Dr. Gitlin: It depends. If the patient is a good historian, it may be clear in the first interview. On the other hand, I've treated patients with "unipolar depression" for two to three years before realizing they had hypomania. One diagnosis to pay close attention to is depression with psychotic features. That often evolves into bipolar disorder, schizoaffective disorder, or schizophrenia (Wood AJ et al, *Front Psychiatry* 2021;12:734272).

TCPR: You sound excited about your work. How do you keep from getting burned out?

Dr. Gitlin: Variety. I see patients, I teach, I do some administrative stuff, I write, and so I'm never doing one thing all the time. Also, I get to see people recover. If I were doing the same thing all day and only saw patients with chronic, treatment-resistant disorders, things might be different.

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