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Chris Aiken, MD
Editor-in-Chief
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Focus of the Month: Dark and Light Therapy

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Learning Objectives

After reading these articles, you should be able to:

1. Identify the strengths and weaknesses behind the claim that vortioxetine (Trintellix) improves cognitive symptoms of depression.
2. Understand how to use dark and light therapy in bipolar disorder and insomnia.
3. Summarize some of the current research on psychiatric treatment.

Trintellix and Cognition: A Closer Look

Michael Posternak, MD. Psychiatrist in private practice, Boston, MA

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

You may have been hearing a lot of buzz about vortioxetine (Trintellix) and cognition. The FDA recently allowed a labeling change with this antidepressant that mentions specific benefits in cognitive symptoms of depression. Depressed patients tell us all the time how bad their memory is, and their concerns are valid. On average, depression impairs cognition to a similar degree as 24 hours of sleep deprivation (Mahableshwarkar AR et al, *Neuropsychopharm* 2016;41(2):2961).

In Summary

- The FDA recently approved a label change to vortioxetine (Trintellix) that cites cognitive benefits with this antidepressant.
- Studies indicate the positive cognitive effects of vortioxetine are gained independently of its antidepressant benefits.
- Vortioxetine's cognitive effects in patients with depression can include benefits in both processing speed and executive function.

Clearly, any antidepressant that improves cognition would be welcome. But we've seen other antidepressants that claim novel benefits, yet fail to

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Light and Darkness in Bipolar Disorder

Jim Phelps, MD

Psychiatrist and author, Corvallis, OR. Creator, psycheducation.org

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

Dr. Jim Phelps is the author of a textbook on bipolar spectrum disorders, *A Spectrum Approach to Mood Disorders: Not Fully Bipolar But Not Unipolar—Practical Management* (W. W. Norton & Company) as well as two self-help books on bipolar disorder. He conducted some of the early studies on dark therapy out of his private practice in Oregon, and we caught up with him to learn about this novel treatment for bipolar disorder.



TCPR: You helped develop a treatment for bipolar disorder that's getting a lot of attention lately. Tell us about this "dark therapy."

Dr. Phelps: People with mood disorders have problems with their circadian rhythm, and regular exposure to light and darkness helps stabilize that rhythm. Timing is key here. Morning darkness can cause depression, and evening light can trigger mania. In dark therapy, people get into darkness in the early evening and stay overnight in a pitch-dark room. So it's kind of the converse of light therapy, where people sit under a bright light in the morning.

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Trintellix and Cognition: A Closer Look

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offer anything unique upon closer scrutiny. So, does vortioxetine really help cognition, and if it does, is it any better than other antidepressants in this regard? Or is this nothing more than a marketing campaign seeking to carve out a new niche for vortioxetine in a crowded antidepressant field? To sort out these questions, we took a close look at the data.

Vortioxetine for depression

Vortioxetine was approved by the FDA for depression in September 2013. Originally called Brintellix, its name was later

changed to Trintellix to avoid confusion with the blood thinner, Brilinta.

For major depression, vortioxetine has established efficacy at daily dosages of 5 mg, 10 mg, and 20 mg in most, but not all, trials. It has also demonstrated efficacy in anxious and elderly patients. Impressively, vortioxetine outperformed the European antidepressant agomelatine in a large, double-blind switch study of patients who failed to respond to an SSRI (Montgomery SA et al, *Hum Psychopharmacol* 2014;29(5):470–482).

Vortioxetine is well-tolerated, with the most commonly reported side effects being nausea, headaches, and dizziness. There is no evidence of ECG changes, it does not seem to cause weight gain, and it may be associated with lower rates of sexual side effects than SSRIs, at least at doses of 5 mg or 10 mg (Jacobsen PL, *CNS Spectr* 2016;2(5):367–378).

OK, so far so good. What about the cognitive data?

Cognitive data

Vortioxetine has a complex mechanism of action. It is a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial antagonist, a 5-HT_{1A} agonist, and an inhibitor of the 5-HT transporter. If that doesn't scream "Cognitive enhancer!" to you, don't worry: It doesn't to anyone else, either. Lab researchers first noted vortioxetine's cognitive-enhancing properties after testing the drug on rats. After this finding, Takeda Pharmaceuticals, the makers of vortioxetine, began to monitor cognition methodically in each of their antidepressant trials. More recently, it was discovered that vortioxetine induces neurogenesis in mice—which, if replicated, could go a long way toward explaining its putative cognitive benefits (Felice D et al, *Front Pharmacol* 2018;12(9):204).

Takeda didn't have much precedent to work with, and they chose the Digit Symbol Substitution Test (DSST) as their primary assessment tool for cognition. The DSST has been around for over a century and is one of the most commonly used tests in neuropsychology. It measures attention, memory, and processing

speed, all areas that are impacted by depression.

What exactly is the DSST? A picture is worth 1,000 words, and with one peek at the test you'll understand exactly how it works. You have to match random symbols with digits as fast as you can. It takes about 2 minutes to administer in practice, and you can check it out at <https://tinyurl.com/yc9oo62k>. As a frame of reference for DSST performance, most depressed patients match 30 to 60 symbols correctly in 90 seconds (mean of 43). Mean scores in healthy adults are 70 in 20-somethings and 49 in those over age 60 (Hoyer WJ et al, *Psychol Aging* 2004;19(1):211–214).

The first evidence that vortioxetine improved cognition in humans came from a study of depressed, geriatric patients, all of whom were free of early signs of dementia. The mean age of the sample was just over 70 years. In this study, 453 subjects were randomized in a double-blind manner to vortioxetine 5 mg, duloxetine 60 mg, or placebo. Both medications treated depression, and both improved verbal learning memory compared to placebo, but only vortioxetine led to significant improvement on the DSST, which suggested that it may confer unique benefits in processing speed and executive function (Katona C et al, *Int Clin Psychopharmacol* 2012;27(4):215–223).

Following this, Takeda conducted a full-court press with a series of large-scale, placebo-controlled trials looking at vortioxetine's effects on cognition. Results on the DSST were positive in 3 out of 5 randomized, controlled trials involving 1,813 depressed patients (Buane BT et al, *Int J Neuropsychopharmacol* 2018;21(2):97–107). It consistently outperformed duloxetine, which was non-significantly better than placebo in terms of DSST results. In the negative studies, vortioxetine trended in a positive direction but ultimately failed to reach statistical significance, possibly because Takeda used a much smaller sample size than in the positive trials (Vieta E et al, *J Affect Disord* 2018;227:803–809).

All of those studies were industry-sponsored, but the methodologies were sound and there were no statistical

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Trintellix and Cognition: A Closer Look

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manipulations that might have led to commercial bias. To their credit, Takeda chose to compare against duloxetine, which had the best cognitive data among antidepressants at the time.

Other antidepressants have not fared as well when run through the DSST. Those were, in order from the least to the most impairing class: SSRIs, MAOIs, and tricyclics. In 9 randomized, controlled trials conducted before the vortioxetine era, these antidepressants failed to improve or actually worsened cognition on this measure. Unfortunately, none of these studies evaluated bupropion, an antidepressant that also has favorable cognitive data (Gualtieri CG et al, *MedGenMed* 2007;9(1):22).

Could vortioxetine's cognitive effects simply be due to its antidepressant benefits? Path analysis shows the two effects

are independent. For example, one study found that 76% of vortioxetine's cognitive benefits are independent of its antidepressant effects (Mahableshwarkar AR et al, *J Clin Psychopharmacol* 2015;76(5):583–591). In contrast, the independence of duloxetine's cognitive effects was estimated at 50%.

To give you a better sense of what vortioxetine's cognitive benefits look like in real life, they're about equal to a 50 mg dose of caffeine, or a shot of espresso. Caffeine improves the DSST performance in healthy volunteers with a medium effect size, about the same as the effect seen with vortioxetine in depressed patients (Jaeger J, *J Clin Psychopharmacol* 2018;38(5):513–519). Does that translate into functional improvement? The DSST is a strong predictor of functioning, but so far only one study has looked at this

outcome, and it found a large effect for vortioxetine and a negligible one for duloxetine (Mahableshwarkar, 2016).

TCPR VERDICT: Takeda Pharmaceuticals has set a new bar for antidepressant research by lining its antidepressant up against one with the best cognitive evidence to date, duloxetine, and rising above it. One key question remains: Will patients actually feel sharper on vortioxetine, and will it, for example, allow them to return to work sooner? Maybe that's a lot to ask, but given its favorable side effect profile, lack of discontinuation syndrome, and clear cognitive benefits, vortioxetine has emerged as a reasonable first-line option for any depressed patient with cognitive complaints.

Expert Interview

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Light therapy is well-established for depression, and there is new research suggesting that dark therapy is very effective in bipolar mania.

TCPR: Where did dark therapy come from?

Dr. Phelps: The idea goes back to the 1990s. Tom Wehr and his colleagues at the National Institute of Mental Health (NIMH) had shown that people sleep better when they're kept in pitch darkness from 6:00 pm to 8:00 am. Now, they knew that insomnia could cause mania, so they tried this dark-room idea in a patient who had intractable rapid cycling. With his consent, they put the patient in a pitch-dark room overnight, from 6:00 pm to 8:00 am. He quickly went from experiencing weekly cycles of mania and depression to a full recovery (Wehr TA et al, *Biol Psychiatry* 1998;43(11):822–828).

TCPR: That's an impressive case. What has the research shown since then?

Dr. Phelps: Next, there was a small controlled trial in hospitalized manic patients. It was only positive in patients whose manias had lasted less than 2 weeks, so we couldn't really conclude that dark therapy worked at that point (Barbini B et al, *Bipolar Disord* 2005;7(1):98–101). Fast forward to 2016, and the first randomized, placebo-controlled trial came out, again in hospitalized mania. The improvements were dramatic over the first week, with a large effect size of 1.9, while the control group barely changed (Henriksen TE et al, *Bipolar Disord* 2016;18(3):221–232).

TCPR: Were there any flaws in that study?

Dr. Phelps: Well, it's just one study, and it was a small one (24 subjects). My opinion, though, is that a treatment that's inexpensive and low-risk ought to have a lower bar of entry for clinical use. The findings still need replication, but if this were a medication that could cause diabetes or raise cholesterol, I'd want to see a lot more confirmation before using it.

TCPR: What about blinding? Didn't the patients know they were getting dark therapy?

Dr. Phelps: That's where it gets interesting. This study used a new type of dark therapy with special glasses that create "virtual darkness." The glasses have an amber tint, and the control group wore glasses with a grayish tint, so the patients couldn't tell which treatment they were receiving. It was the raters who weren't completely blinded. To rate manic symptoms in a 24-hour period, they incorporated input from the hospital staff, and those staff knew what the amber-colored glasses meant. There was one blinded assessment, though: actigraphy. Mania is a hyperactive state, so wrist actigraphy is increasingly used to measure it. The dark therapy group had a significant drop in their overactivity.

“Reducing blue light seems to deepen sleep and help people fall asleep earlier. I recommend patients with insomnia wear blue light-blocking glasses 1 to 2 hours before bed. They don't have a sedative effect, however, so you have to manage expectations in insomniacs who may be hoping to be knocked out.”

Jim Phelps, MD

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Expert Interview
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TCPR: Tell us more about these amber glasses.

Dr. Phelps: There's a story there, and it also begins in the 1990s: with the discovery of melanopsin. This is a photoreceptor in the eye, but instead of connecting to the visual cortex, melanopsin connects to the suprachiasmatic nucleus, which regulates the biologic clock. Its whole purpose is to tell the brain whether it's light or dark outside. And here's the twist—melanopsin only responds to blue light, so if we block that wavelength, the brain will think it's in pitch darkness. Eliminating blue light triggers changes in the brain that set the stage for sleep, like raising melatonin.

TCPR: How do you eliminate blue light?

Dr. Phelps: That's what the amber glasses do. Around 15 years ago, I came across this research and wondered if there was a way to create dark therapy by eliminating blue light. It turns out that evening blue light is linked to other health problems, like breast cancer. There's a company, www.LowBlueLights.com, that makes amber-tinted glasses that block blue light for medical purposes. They graciously gave me many pairs to try out in a series of bipolar patients in my private practice. (*Editor's note:* Dr. Phelps does not have financial interests in specific products.)

TCPR: What did you find?

Dr. Phelps: These were outpatients, and they were relatively stable, with some hypomania, mixed states, and a lot of insomnia going on. About half of them came back and said, "Wow, when I wear these for a couple of hours before bed, I sleep better. I go to sleep sooner, like an hour sooner." They were really impressed. The other 50% said, "Nah, interesting idea, but these don't do anything" (Phelps J, *Med Hypotheses* 2008;70(2):224–229).

TCPR: Walk us through dark therapy.

Dr. Phelps: Basically, patients have to be in real darkness or virtual darkness overnight. There are three ways to do this. They can be in a pitch-dark room, or if the lights are on they can wear blue light-blocking glasses. Patients can also use special blue-free light bulbs, as long as the room is otherwise pitch-dark. These are lights that don't emit any blue wavelengths; they emit a sort of yellow-colored light. There are also ways to reduce blue light in devices, through special settings or apps, but they don't completely eliminate the blue light. Those may be good for general health, but they're not going

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Ask the Editor

Each month, Editor-in-Chief Chris Aiken, MD, gives advice on a different practice challenge.

CBT for Insomnia

Dear Dr. Aiken: The January 2019 issue mentioned cognitive behavioral therapy for insomnia (CBT-i) as a good alternative to sleep meds. It's hard to find a therapist trained in CBT-i in my area. Are there any evidence-based self-help options that I can recommend to my patients?

Dr. Aiken: Certified therapists are listed online at www.behavioralsleep.org, but they are few and far between. To bridge this gap, there's been a lot of research on self-guided CBT-i, and the outcomes suggest it works about as well as the live version (Zachariae R et al, *Sleep Med Rev* 2016;30:1–10). I've collected some of the better-researched programs in the table. My top two options, Sleepio and SHUTi, are on a temporary hiatus and are absent from the table. These programs recently closed their doors to the general public so they can pursue FDA approval as digital therapeutics.

The day may soon come when we're prescribing CBT-i apps instead of Ambien, and I'll welcome that. Treatment guidelines already place CBT-i above hypnotics as the gold standard for insomnia. Safety is one reason, but there's also evidence that CBT-i is more effective over the long term (Beaulieu-Bonneau et al, *Sleep* 2017;40(3):zsx002). The therapy includes basic sleep hygiene, like avoiding daytime naps, but goes a few steps beyond that. At its core is a structured program of sleep restriction where patients raise their sleep drive by limiting their time in bed. A brief manual is available online at <https://tinyurl.com/ycptj345>.



CBT for Insomnia: Self-Guided Options

Program	Details	Cost
Restore http://restore.cbtprogram.com	Offers computerized CBT-i as well as other cognitive-behavioral modules.	\$125, one time
CBT for Insomnia www.cbtforinsomnia.com	Old-school PDF and MP3 format. Allows users to contact a therapist in the premium version. Based on a proven approach, but not independently tested.	\$50–\$70, one time
CBT-i Coach	This app was designed to be used with a therapist, but a motivated patient can benefit from it solo. Created by the VA, but suitable for civilians.	Free
Books	<i>Say Good Night to Insomnia</i> by Gregg Jacobs (Holt Publishing, 2009); <i>End the Insomnia Struggle</i> by Colleen Ehrnstrom and Alisha Brosse (New Harbinger Publications, 2016)	\$10–\$20

Expert Interview
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to cut it for dark therapy (see “Dark Therapy Devices” table on page 5).

TCPR: What about the timing?

Dr. Phelps: For full mania, the dark protocol extends from 6:00 pm to 8:00 am. That’s hard for patients to stick to, so I’ll involve family or friends if they’re not in the hospital. Once the patient recovers, the darkness can start at a later time, like 8:00 pm to 10:00 pm. In my experience, you can start at that later time in mild cases, and adherence is a lot better when patients don’t have to wear the glasses so early in the evening.

TCPR: Do you ever start earlier than 6:00 pm?

Dr. Phelps: No. That could worsen mood by disrupting the circadian rhythm. It’s worth warning patients about this. Some find the blue-light blockers calming and start wearing them all day long.

TCPR: Are there any side effects?

Dr. Phelps: Possibly depression. In the hospital study, 2 patients developed depression with the amber lenses. It remitted when the lenses were either delayed from 6:00 pm to later in the evening or just stopped entirely. I’ve seen that in my own practice, but then again I’ve seen that with just about any anti-manic therapy when it’s given too aggressively. Headaches have also been reported.

TCPR: How does the world look through these glasses?

Dr. Phelps: It’s still bright, but everything has a warm, yellow glow. Think fireside, starlight, candlelight—that’s the type of light our species evolved under at night for thousands of years. It’s only been in the past century, and more so the past decade, that blue light has made its way into the evening hours. Smartphones, LED screens, TVs, and energy-efficient bulbs are the main sources. Those smartphones may be small, but when you hold them close to your face, it can suppress melatonin as much as a large-screen TV that’s on the other side of the room.

TCPR: Are people with bipolar disorder the only ones affected by this?

Dr. Phelps: No, but they have to be more careful than the rest of us because anything that disrupts sleep can set off new episodes. They’re not completely alone, though, as nocturnal light takes a toll on general health. It worsens concentration the next day, and raises the risk of breast cancer, obesity, heart disease, and diabetes. It’s also linked to depression. In the largest study, sleeping with a dim light in the bedroom, like a nightlight, nearly doubled the risk of depression over 2 years.

It wasn’t a controlled study, but the animal data on this are so strong that controlled studies of nocturnal light are considered to be unethical in humans (Obayashi K et al, *Am J Epidemiol* 2018;187:427–434).

TCPR: How do your patients get their rooms pitch-dark?

Dr. Phelps: I begin by asking, “How much light is there in your bedroom?” Lots of people live near a street light, and blackout curtains can help with that. Some of my patients use tinfoil on the inside of the window. An eye mask can help if they’re not able to get the room dark enough.

Does Mania Follow the Sun?

If dark nights can treat mania, can too much sunshine destabilize it? Yes and no. Mania is linked to rapid changes in sunlight, but not to the amount of light itself. Mania peaks in early spring when there’s a steep rise in sunlight. By the time the longest day of the year comes along in late June, there’s no longer a detectable increase in mania (Parker G et al, *J Affect Disord* 2018;226:72–76).

In some regions, this change in spring sunlight is particularly dramatic, and the onset of bipolar disorder tends to be earlier in patients who grew up in those areas (Bauer M et al, *Acta Psychiatr Scand* 2017;136:571–582). The spring effect is strongest in the Sunbelt and in the Northwest and Northern Midwest. The flux in sunlight peaks between March and April in most areas of the US, but in the Northeast, from DC to Maine, it’s between April and May. To see where your city lies, check www.thecarlatreport.com/springmania.

As a bipolar specialist, my phone rings off the hook when spring arrives, but the urgency has cooled a bit since learning about dark therapy from Dr. Phelps. I keep a pair of blue light-blocking glasses on my desk for demonstration, and remind patients to start wearing them—preventatively—as the days begin to lengthen in late February. As Dr. Phelps describes, the best time to don them depends on the severity of symptoms. For prevention, it’s 1 to 2 hours before bed.

—Chris Aiken, MD.

Dark Therapy Devices	
Blue Light-Blocking Glasses	
These models were tested in clinical studies. Most other options don’t block enough of the blue.	<ul style="list-style-type: none"> Uvex (\$7–10 on Amazon): Ultraspec 2000 model S0360X and Skyper model S1933X Any model at www.LowBlueLights.com (\$50)
Blue-Free Bulbs	
Sleep-friendly bulbs that won’t disturb melatonin.	<ul style="list-style-type: none"> Any option at www.LowBlueLights.com Bulbs: SCS Nite-Nite Light Bulb, Lighting Science GoodNight Sleep Nightlights: Maxxima MLN-16 Amber LED (\$15)
Apps	
These reduce the blue light emitted by electronic devices, but not enough to qualify for dark therapy.	<ul style="list-style-type: none"> Apple: Candlelight, Night Mode Windows: JustGetFlux.com Android: Twilight and Blue Light Filter Kindle: BlueShade

Research Updates IN PSYCHIATRY

ALCOHOL

Prazosin for Alcohol Use Disorders

REVIEW OF: Simpson TL et al, *Am J Psych* 2018; <https://doi.org/10.1176/appi.ajp.2018.17080913>

TYPE OF STUDY: Randomized, placebo-controlled trial

Prazosin is often used as a second-line option for a broad array of psychiatric conditions, including anxiety, insomnia, nightmares, and post-traumatic stress disorder (PTSD). It is a high blood pressure medication that also modulates the stress-response system through noradrenergic effects, blocking alpha-1 receptors in the brain. Since stress is a common trigger for excessive drinking, this study set out to test whether prazosin could improve sobriety in alcohol use disorders.

Eighty subjects with alcohol use disorders were randomized to receive either prazosin or placebo. Subjects with PTSD were excluded in order to isolate the potential benefits of prazosin for drinking directly. Prazosin was titrated up to a target dosage of 16 mg/day, as tolerated. All subjects were actively drinking at the start of the study, and they reported their daily alcohol consumption and cravings for the previous day through a toll-free interactive voice system during the 12-week study. Assessments were double-blind, and the primary outcomes were: (1) number of *drinks* per week, (2) number of *drinking days* per week, and (3) number of *heavy drinking days* per week.

Compared to placebo, those receiving prazosin reported fewer drinks (mean decrease of 8.0 vs 1.5 drinks per

week; $p = 0.03$) and fewer number of heavy drinking days (mean decrease of 0.8 vs 0.3 days per week; $p = 0.01$), though the number of drinking days was no less with prazosin. Drowsiness and edema were the only two side effects associated with prazosin.

TCPR'S TAKE

Given its relatively benign side effect profile and established track record, prazosin can already be considered a reasonable second-line option for alcohol use disorders. For patients with any combination of anxiety, insomnia, nightmares, PTSD, or hypertension, prazosin is an even more appealing option.

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

Expert Interview

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TCPR: What about television in the bedroom?

Dr. Phelps: That's a tough one. People with depression don't like to lie in the dark with their own thoughts, so they will do things in order to avoid that. Often they will stay awake with lighting devices, such as televisions or screens of various kinds, which then delays their sleep. For many patients, a pair of earbuds with music, radio, or podcasts will have the same effect. UCLA's Center for Meditative Studies has free programs that are very good for helping to calm the mind (www.uclahealth.org/marc/audio).

TCPR: Can blue-light blockers help insomnia?

Dr. Phelps: The studies are small, but reducing blue light seems to deepen sleep and help people fall asleep earlier. However, they don't have a sedative effect, so you have to manage expectations in an insomniac who may be hoping to be knocked out by them. I recommend patients with insomnia wear them 1 to 2 hours before bed (Shechter A et al, *J Psychiatr Res* 2018;96:196–202).

TCPR: What about in depression?

Dr. Phelps: They might help there, but the studies are small and the results have been mixed. There was a positive study in postpartum depression, where the women wore blue-light blockers when they got up to nurse their child (Bennett S et al, *Med Hypotheses* 2009;73:251–253). The negative trial was in depressed patients with insomnia, but the glasses they used were uncomfortable, so compliance was a big issue (Esaki Y et al, *Chronobiol Int* 2017;34(6):753–761). What I recommend for depression is morning light.

morning light.

TCPR: I imagine that's hard to get with blackout curtains on.

Dr. Phelps: Yes, and morning light is also dim in the wintertime and for anyone living north of the 30th–40th latitude, which is most of the U.S. above Texas or Georgia. This is where dawn simulators are helpful. They create a virtual sunrise in the bedroom, and they've worked for winter depression in a handful of small, controlled studies. They aren't as powerful as a lightbox, but they are risk-free, low-cost, and easy to use.

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Dawn Simulators

All-in-One Lamps

Lamp, bulb, and time, all in one.	<ul style="list-style-type: none"> NatureBright L6060 PER2 LED (naturebright.com) Philips Morning Wake-Up Light HF3500, HF3510, HF3520
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Timers

These plug into a lamp and require dimmable bulbs.	<ul style="list-style-type: none"> LightenUp (windhovermfg.com) SunRise Controller BioBrite
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Apps

These turn on the smartphone's flashlight. They may not be bright enough to treat depression, but they are cheap and portable.	<ul style="list-style-type: none"> Rise & Shine Lichtwecker
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CME Post-Test

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

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

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

- The dark therapy protocol for bipolar mania requires that the patient be in real darkness or virtual darkness overnight from _____. (LO #2)
 - 5:00 pm to 6:00 am
 - 6:00 pm to 6:00 am
 - 6:00 pm to 8:00 am
 - 7:00 pm to 7:00 am
- According to a recent study, patients on either vortioxetine or duloxetine showed the same improvements in both depression and cognition as measured by the Digit Symbol Substitution Test (DSST). (LO #1)
 - True
 - False
- How long before bedtime does Dr. Phelps recommend patients with insomnia wear blue light-blocking glasses? (LO #2)
 - 30 minutes
 - 1 to 2 hours
 - 1 hour every other day
 - 3 to 4 hours
- The cognitive benefits of vortioxetine are comparable to which of the following? (LO #1)
 - Vyvanse: 30 mg dose
 - Adderall: 30 mg dose
 - Caffeine: 50 mg dose
 - Caffeine: 100 mg dose
- In a 2018 study, patients taking 16 mg/day of prazosin reported both fewer drinks and fewer days of heavy drinking compared to placebo. (LO #3)
 - True
 - False

News of Note

An Opioid Combo Falls Short in Depression

Opioids have a bad name these days. But let's not forget that they were once considered a first-line treatment for depression before the discovery of MAOIs and tricyclics in the 1950s. That history has been revived recently by buprenorphine, a partial opioid agonist that was fast-tracked by the FDA for treatment-resistant depression. Buprenorphine showed promise in early studies, where it reduced both depression and suicidality. The effect was rapid, much like we see with ketamine, which may also work through the opioid system (see Research Update in *TCPR*, Jan 2019).

In the end, the FDA handed this novel therapy a thumbs down. The issue was not safety but efficacy,

although there were also concerns that short-term trials might not be adequate to assess the addictive liability of buprenorphine.

The manufacturer submitted 4 trials, but only 2 of those trials had positive results, and there were several flaws in the data. The company switched the primary outcome measures after their initial choices failed; they relied on averaged ratings from each time point instead of the final score; and they abbreviated the main rating scale, the MADRS, in ways that appeared to bias the results. Buprenorphine acts differently at high (8 mg) and low (2 mg) doses, but that did not appear to be the issue—neither dose worked well in these studies.

Buprenorphine remains available as Suboxone, which is FDA-approved for opioid dependence and became generic in June 2018. However, there is an important difference between Suboxone and its antidepressant cousin that failed to make it to market. Both drugs combine buprenorphine with an opioid antagonist to prevent abuse. Suboxone uses naloxone, a broad antagonist, while buprenorphine is paired with samidorphan, which selectively antagonizes the mu-opioid receptors. Samidorphan is not currently available, but we may hear from it again. It is undergoing phase II studies as a combo pill with olanzapine in hopes that it will curb the weight gain on that antipsychotic.

—Chris Aiken, MD.

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This Month's Focus:
Dark and Light Therapy

**Next month in *The Carlat Psychiatry Report*:
Parenting, Pregnancy, and Prevention**

Expert Interview
Continued from page 6

My standard recommendation is LightenUp, which makes affordable models for \$15 to \$30 (see "Dawn Simulators" table on page 6).

TCPR: Can they be used with dark therapy?

Dr. Phelps: Yes. They have no risk of causing mania. Patients program the device for the time they want to wake up. It then turns on gradually in the 30 to 60 minutes before the specified wake-up time. People tend to feel more alert when they wake up to these because it lifts them gradually out of deep sleep. By turning on at the same time each day, a dawn simulator can help keep the circadian rhythm in line.

TCPR: How important is regular timing in bipolar disorder?

Dr. Phelps: Very important. I see dark therapy and light therapy as part of a broader approach to bipolar disorder that involves regulating circadian rhythms. That's the goal of social rhythm therapy (SRT), a psychotherapy with good evidence in bipolar. SRT helps patients identify and regulate key events that help set their circadian rhythm and stabilize their mood. Light and darkness are important, but so are physical activity, meal times, and contact with people. It's the timing of these things that matters in bipolar disorder.

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

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