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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Mood Disorders

Learning Objectives

After reading these articles, you should be able to:

1. Understand the role of light therapy to improve sleep and as first-line treatment for seasonal affective disorder.
2. Identify four ways that bipolar disorder can mimic ADHD.
3. List the pros and cons of various antipsychotics in the treatment of obsessive-compulsive symptoms.
4. Summarize some of the current research findings on psychiatric treatment.

Light Therapy: Good for What Ails You?

Edmund M. Higgins, MD. Clinical associate professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina.

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

Highlights From This Issue

Antipsychotics can both treat and exacerbate OCD symptoms. Dr. Michael Poyurovsky names a few that are more favorable in patients with schizophrenia and OCD.

Light therapy is first-line in winter depression and has potential in bipolar depression, ADHD, bulimia, PTSD, sleep, and arthritis.

Lurasidone may need higher dosing in schizophrenia, and some antipsychotics are unlikely to help in mania.

There are several lifestyle changes with broad health benefits that we often encourage in our patients. Exercise, a healthy diet, sleep hygiene, and supportive social connections are near the top of the list, and bright daytime light might be worth adding. Light therapy is a standard treatment for seasonal affective disorder, and in this article we'll look at other potential uses for this novel treatment.

An expanding role in depression

In 1984, Norman Rosenthal and colleagues at the NIMH coined the term seasonal affective disorder (SAD) (Rosenthal NE et al, *Arch Gen Psych* 1984;41(1):72–80). They described patients who, year after year, had depression in the fall and winter that cleared up in the spring. The authors were able to show that extending the daylight hours with artificial bright light during the

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Q&A With the Expert

The Schizophrenia-OCD Overlap
Michael Poyurovsky, MD

Ma'ale HaCarmel Mental Health Center, Tirat Carmel, Israel; Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel.

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

TCPR: What is schizo-obsessive disorder?

Dr. Poyurovsky: Schizo-obsessive disorder (schizo-OCD) is not a DSM diagnosis. The term is used to refer to patients with schizophrenic disorders that have comorbid features of OCD. We see these obsessive-compulsive symptoms in schizophrenia more often than would be expected by chance. About one in four patients have them, although only about half of those patients actually meet the full DSM-5 criteria for OCD. Often the OCD symptoms decrease during acute psychosis, so you are more likely to see them between psychotic episodes. It's important to recognize schizo-OCD since functional outcomes are worse for these patients (Poyurovsky M. *Schizo-Obsessive Disorder.* New York, NY: Cambridge University Press; 2013).

TCPR: How does the presentation differ from classic OCD?

Dr. Poyurovsky: Many of these patients have classic OCD symptoms, but there is a subgroup of around 10%–20% whose obsessions and

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Expert Interview
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compulsions are intertwined with their psychotic symptoms. For example, compulsive behaviors are driven by psychotic delusions, such as voices telling them to wash their hands. These patients might not complain of the compulsions because they are not aware of them. This differs from classic OCD, where patients usually have some awareness that their obsessions and compulsions are irrational.

The Antipsychotic-OCD Controversy

TCPR: I've heard that antipsychotics can cause OCD, and I've also heard that they can treat OCD. What is going on there?
Dr. Poyurovsky: Yes—this goes both ways. We have many controlled trials where antipsychotics improved OCD, but they can also cause or exacerbate it, particularly clozapine and to a lesser extent olanzapine. My best estimate is that clozapine causes OCD in 10%–15% of cases, and this risk may be dose dependent. We published open-label reports of clozapine improving schizo-OCD in the 150–300 mg/day dose range, but when titrated beyond that, clozapine has the opposite effect of provoking OCD (Poyurovsky M, *Isr J Psychiatry Relat Sci* 2008;45(3):219–220; Poyurovsky M et al, *Clin Neuropharmacol* 1996;19(4):305–313).
TCPR: Is it just in schizophrenia that we see this effect, or can antipsychotics trigger OCD in anyone?
Dr. Poyurovsky: It seems to be a drug effect rather than an association with schizophrenia itself. Antipsychotics can cause obsessive-compulsive symptoms in schizophrenia, bipolar disorder, and some other psychotic disorders.

TCPR: Which antipsychotics are less likely to cause OCD?
Dr. Poyurovsky: There are some data on aripiprazole, as well as amisulpride, but that medication is only available in Europe. Both of these antipsychotics have limited 5-HT2A serotonergic antagonism, which suggests they have a low potential for causing OCD (Schirmbeck F et al, *J Psychopharmacol* 2013;27(4):349–357).
TCPR: Is 5-HT2A antagonism the mechanism through which antipsychotics cause OCD?
Dr. Poyurovsky: We don't have the evidence, but the impression is that the more 5-HT2A serotonin antagonism you have with an increased dose, the more of an OCD-provoking effect.
TCPR: So serotonin 5-HT2A antagonism might cause OCD. Can dopamine antagonism treat OCD?
Dr. Poyurovsky: Yes. The most solid evidence is the therapeutic efficacy of augmentation with low-dose D2 dopamine receptor antagonists in patients with severe, classic OCD, primarily with risperidone and haloperidol. By low dose, I would say 2.5 mg of haloperidol and 2–3 mg for risperidone. Other antipsychotics have positive trials in OCD as well, like aripiprazole, olanzapine, paliperidone, and quetiapine, and these have broader effects beyond the dopamine system that might explain their benefits (Zhou DD et al, *J Psychiatr Res* 2019;111:51–58). On the other hand, dopamine agonists like pramipexole can trigger OCD symptoms.
TCPR: Are there other 5-HT2A antagonists that we should worry about in schizo-OCD?
Dr. Poyurovsky: Mirtazapine, for example, is a very important 5-HT2A antagonist. There are some cases where it seems to provoke OCD, and at a minimum, mirtazapine is not going to treat OCD.

Other Treatments

TCPR: Do patients with schizo-OCD respond to SSRIs?
Dr. Poyurovsky: In general, schizo-OCD is difficult to treat. I would consider an SSRI in schizophrenia only when the symptoms are typical for OCD and their severity reaches a threshold for clinical significance. SSRIs should be added only in stabilized antipsychotic-treated patients during remission, not during acute psychosis. My impression is that lower doses are often sufficient, as opposed to the high doses we typically use in "pure" OCD. However, the evidence base is still lacking.
TCPR: Why not start SSRIs during acute psychosis? What is the risk?
Dr. Poyurovsky: Clinical experience suggests that antidepressants may cause psychotic exacerbation and manic symptoms, especially when there is concurrent bipolarity, such as in schizoaffective disorder. Patients with a history of impulsivity and aggressiveness may also be at risk for psychotic exacerbation on SSRIs. Akathisia is another concern. Patients with schizo-OCD are more vulnerable to this side effect, which can happen on SSRIs as well as antipsychotics. The bottom line is that we should use the lowest effective dose, only add an SSRI when the patient's active psychotic symptoms are in remission, and continuously monitor for risks like akathisia and psychosis.
TCPR: Are there other risks with SSRIs?

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Light Therapy: Good for What Ails You?
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winter had an antidepressant effect. That pilot study has since been confirmed in over three dozen controlled trials, most of which used a dim light box as the placebo. Light therapy worked as well as an antidepressant in head-to-head studies and is considered first-line in the treatment of SAD (Geoffroy PA et al, *Sleep Med Rev* 2019;48:101213).

The success in SAD motivated researchers to explore light therapy for other psychiatric disorders, starting with nonseasonal depression. 23 controlled trials have concluded that light therapy works in this population, even when delivered in summer (Geoffroy et al, 2019). The treatment can augment and accelerate antidepressants and TMS. Light therapy also works in several populations where antidepressants are not always ideal: pregnant women, adolescents, traumatic brain injury, and bipolar depression (Campbell PD et al, *Einstein J Biol Med* 2017;32:E13–E25; Srisurapanont K, *PLoS One* 2021;16(2):e0246172).

Pocket Protocol for Light Therapy

First-line use	Seasonal affective disorder (start two weeks before typical onset of depression, then taper off over two weeks in the spring)
Second-line use	Nonseasonal depression, bipolar depression, antidepressant augmentation, depression after traumatic brain injury, shift work disorder, insomnia, delayed sleep phase disorder
Third-line use	Any season: PTSD, fibromyalgia Winter use: ADHD, bulimia, sexual dysfunction in men
Reliable brands	Carex Day-Light Classic or Classic Plus ($120) Northern Light Technologies BOXelite OS ($200)
Specs	Intensity: 10,000 lux is optimal, less than 3,000 lux is ineffective Screen size: at least 12" x 15" Wavelength: white light (around 509 nm)
Start time	Depression and other disorders: early morning (5:00–8:00 am; can use AutoMEQ rating scale at www.cet.org to determine ideal time) Bipolar depression: midday (12:00–2:00 pm) Insomnia: 4:00–5:00 am
Duration	30–120 minutes, with longer duration for treatment-resistant cases or boxes with < 10,000 lux. In bipolar disorder, titrate gradually to prevent mania (start 15 minutes/day, raise by 15 minutes each week toward 60 minutes)
Positioning	Sit so the bottom third of the box is at eye level, then tilt the box so it hovers at an angle of 30–45 degrees over your head, keeping your eyes within 12–14 inches of the box; you can read, eat, or use a laptop while under it
Warnings	Do not use after 2:30 pm (or it will disrupt circadian rhythms) Do not look directly into the box (angle eyes downward) Glasses are OK, but do not wear sunglasses or a hat during light therapy
Troubleshooting	For difficulty waking up, use a dawn simulator (see *TCPR*, Jan 2019)
Risks	Patients with glaucoma, cataracts, or retinopathy should be under the supervision of an ophthalmologist Caution with photosensitive conditions (eg, systemic lupus erythematosus) or when taking photosensitive medications (eg, lamotrigine, tricyclics, antipsychotics)
Side effects	Headache, eye strain, nausea, insomnia

Sleep and circadian rhythms

Light regulates the circadian rhythm, and morning light therapy helps night owls with delayed sleep phase disorder fall asleep earlier. In primary insomnia, it improves daytime energy, boosts sleep quality, and helps patients fall asleep faster (van Maanen A, *Sleep Med Rev* 2016;29:52–62). Some of the most robust findings for light therapy on insomnia have been in older adults with cognitive impairment, dementia, or Parkinson's disease. There, light therapy was shown to improve sleep as well as mood and behavioral disturbances, but had only a limited effect on cognition and quality of life (Cibeira N et al, *Geriatric Nurs* 2020;41(6):970–983).

When treating sleep disorders, timing is important, as the therapy works best delivered early in the morning for 30–120 minutes, ideally just after the circadian drop in temperature that occurs around 4:00 am. Brighter light (5,000–10,000 lux) is more effective for sleep. This morning light can be augmented with evening darkness (see Feb 2019 *TCPR*'s interview with Jim Phelps on blue light–filtering glasses and dark therapy for insomnia).

Shift workers also benefit by turning on a light box in their darkened mornings and creating an artificial evening at the end of their day with blackout curtains and blue light–filtering glasses. Similar manipulations of light and darkness can also alleviate jet lag (see April 2019 *TCPR*'s "Ask the Editor" for a jet lag protocol).

Other uses

Circadian rhythms have broad biological effects, stretching from mood to cardiac function and metabolic health. Appetite follows seasonal patterns, and winter light therapy reduced binge eating in bulimia nervosa in small controlled trials (Braun DL et al, *Compr Psychiatry* 1999;40(6):442–448). Testosterone declines in winter, which may explain why winter light therapy improved libido in men with sexual dysfunction (Bossini L, *Psychother Psychosom* 2009;78(2):127–128).

ADHD symptoms are also known to worsen in winter in some patients. In an open label trial of morning light therapy in the fall and winter, light therapy improved objective and subjective symptoms of ADHD. These benefits were independent of mood and instead were associated with a shift toward earlier bedtimes, which is interesting as one in four patients with ADHD have delayed sleep phase disorder (Rybak YE et al, *J Clin Psychiatry* 2006;67(10):1527–1535).

Recently, morning light therapy reduced core symptoms of combat-related PTSD in a placebo-controlled trial where the treatment was delivered across all seasons. Unlike the ADHD study, the benefits in PTSD were unrelated to changes in sleep or circadian rhythms (Youngstedt SD et al, *Mil Med* 2021;usab014).

Outside of psychiatry, light therapy improved back pain and fibromyalgia in small controlled trials, an effect that may be mediated by its sleep benefits. Although metabolic health is influenced by circadian rhythms, light therapy recently failed in the first randomized controlled

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Expert Interview

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Dr. Poyurovsky: Yes. You also have to look at the pharmacokinetic interactions between antipsychotics and SSRIs. Fluvoxamine (Luvox), fluoxetine (Prozac), and paroxetine (Paxil) can raise some antipsychotic levels two- to 10-fold. Escitalopram (Lexapro) is not FDA approved for OCD, but it may be considered as an off-label choice in schizo-OCD patients because it lacks those drug-drug interactions (Stryjer R, *Int Clin Psychopharmacol* 2013;28(2):96–98).

TCPR: And what about clomipramine?

Dr. Poyurovsky: Clomipramine should be reserved for the next step—after failure of an SSRI—because it produces prominent hallucinogenic serotonergic effects and cardiotoxicity. One combination I would avoid in particular is clomipramine and clozapine, because both can cause cardiac arrhythmias, lower seizure threshold, and—in rare cases—paralytic ileus (Margetić B et al, *Psychopharmacol Bull* 2008;41(2):9–11).

"We have many controlled trials where antipsychotics improved OCD, but they can also cause or exacerbate it, particularly clozapine and to a lesser extent olanzapine."

Michael Poyurovsky, MD

TCPR: Are there other pharmaceutical options for schizo-OCD?

Dr. Poyurovsky: In 2008 we published a small trial of lamotrigine in patients who had schizophrenia and schizoaffective disorder with OCD. We found it efficacious for OCD as well as depressive symptoms after titrating to a dose of 200 mg/day (Poyurovsky M et al, *J Psychopharmacol* 2010;24(6):861–866). That was an open-label study, but the concept was later supported by two randomized controlled trials of lamotrigine in classic, pure OCD where it augmented SSRIs (Bruno A et al, *J Psychopharmacol* 2012;26(11):1456–1462).

TCPR: What are some challenges to using cognitive behavioral therapy (CBT) in schizo-OCD?

Dr. Poyurovsky: CBT should be considered in schizo-OCD only when the psychosis has stabilized and the patient has typical OCD symptoms. CBT would be particularly appropriate for patients who are compliant with treatment, who have good insight into their OCD symptoms, and who are capable of understanding cognitive therapy and ready to be involved with it, which is not easy for a lot of patients with schizo-OCD.

Diagnostic Tips

TCPR: How do you screen for OCD in schizophrenia?

Dr. Poyurovsky: I start with the typical questions used to identify OCD, screening for common dimensions of OCD. I'll ask questions like "Do you keep checking things over and over again?", "Do you repeatedly wash your hands?", and "Do you have repetitive intrusive thoughts that you perceive as unwanted and would like to get rid of?"

TCPR: Do you run into things that obscure the diagnosis?

Dr. Poyurovsky: Yes. There are a few areas where symptoms of schizophrenia and OCD overlap and it can be difficult to tell them apart. For example, psychotic *content* may take an obsessive-compulsive *form*, as when a patient said to me, "It seems like my neighbors are watching my every move when I smoke on the balcony, so I am very conscious of this and try to handle myself perfectly. When I am doing something different, like moving my body too much in one direction, I then have to look at my neighbors' windows and blink my eyes 10 times. Otherwise the paranoia gets worse." In a case like that, I would not diagnose OCD because it is exclusively related to delusional content. I would wait and reassess after the psychosis resolves. There are other areas where we see overlap.

TCPR: Such as?

Dr. Poyurovsky: Obsessional doubt may be mistaken for schizophrenic ambivalence. OCD-related compulsions can resemble the manneristic, stereotypical behaviors that are common in schizophrenia. Akathisia can also be associated with repetitive OCD-like behaviors. For example, if your patient starts to ask you repetitive questions despite your repetitive answers, it might be akathisia. Then again, patients with schizo-OCD are also more prone to extrapyramidal symptoms and akathisia.

TCPR: DSM-5 recognizes OCD "with poor insight." How do we tell the difference between that and schizophrenia?

Dr. Poyurovsky: One of the most important things is to identify the primary disorder. Is it primary OCD with some schizophrenia spectrum components like schizotypal disorder? Or is schizophrenia the primary disorder with OCD as a comorbidity? This is extremely challenging because in most patients the OCD symptoms begin before the psychotic symptoms. OCD tends to begin in childhood, but if it progresses to schizophrenia during adolescence, I would see schizophrenia as the primary diagnosis.

TCPR: I would also imagine that negative symptoms are more prominent in schizo-OCD than in pure OCD with poor insight.

Dr. Poyurovsky: Yes. Amotivation, flat affect, and other negative symptoms, as well as disorganized behavior and cognitive dysfunction, help to establish the correct diagnosis of schizophrenia. Family history can help too. We conducted a study on this and found higher rates of OCD, obsessive-compulsive personality disorder, and schizo-OCD in the family histories of patients with schizo-OCD, but not in the families of patients with pure schizophrenia (Poyurovsky M et al, *Am J Med Genet B Neuropsychiatr Genet* 2005;133B(1):31–36).

TCPR: Do you also see an association of OCD with other disorders?

Dr. Poyurovsky: Yes. In the past my impression was that due to pathophysiological and clinical linkage between OCD and schizophrenia, there is some "affinity" between the two disorders. Now I have a different impression—the prevalence of OCD in bipolar disorder is very substantial, around 10%–20%, particularly in bipolar depression (Ferentinos P et al, *J Affect Disord* 2020;263:193–208; Braverman L et al, *Psychiatry Res* 2021;302:114010).

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

To learn more, listen to our 10/11/21 podcast, "Can Antipsychotics Worsen OCD?" Search for "Carlat" on your podcast store.

How to Diagnose ADHD in Bipolar Disorder

Chris Aiken, MD. Editor-in-Chief of TCPR. *Practicing psychiatrist, Winston-Salem, NC.*

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

Hailey is a 24-year-old woman with bipolar II disorder who has recently come out of a mixed episode. Although her mood symptoms have resolved, she is distracted easily, has difficulty organizing her work, and often forgets important tasks. She read about ADHD online and asks if she can have a stimulant to help her focus.

ADHD and hypomania share many symptoms in common: distraction, hyperactivity, impulsivity, irritability, and excessive talking. In theory these symptoms are episodic in bipolar disorder and continuous in ADHD, but in practice that separation is not so clean. In this article I'll present a more nuanced guide to this vexing diagnosis.

ADHD and bipolar disorder can genuinely occur together, and they do so in 10%–20% of bipolar patients. But bipolar disorder can also cause symptoms that mimic ADHD, which is why 30%–50% of bipolar patients who screen positive for ADHD on a self-reported questionnaire do not turn out to have ADHD after a structured interview (Torres I et al, *Acta Psychiatr Scand* 2015;132(5):389–399).

The table below lists four ways that bipolar disorder can mimic ADHD, starting with the manic or hypomanic episodes themselves. These episodes are relatively easy to distinguish from ADHD by their episodic nature and lack of early childhood onset. A more difficult rule-out is persistent cognitive dysfunction due to the neuroprogression of bipolar disorder itself. Each episode in bipolar disorder can take a toll on the brain, causing ADHD-like symptoms of inattention, disorganization, and executive dysfunction. Unlike ADHD, these cases are marked by memory problems and mental slowing, and they usually lack the restless, frenetic energy of ADHD. More importantly, these cognitive deficits follow an opposite course to ADHD. They start in adulthood and worsen with time, while ADHD begins before age 12 and tends to improve in adulthood.

Causes of ADHD Symptoms in Bipolar Disorder

Cause	Similarity to ADHD	Difference From ADHD	Prevalence in Bipolar
Manic/ hypomanic episodes	Symptom overlap (distracted, hyper, irritable, talkative)	In bipolar, these symptoms are usually episodic and occur with other mood symptoms	100%
Cognitive deficits of bipolar disorder	Cognitive problems persist long after the mood episode resolves	Lack of childhood onset	30%–60%
Hyperthymic temperament	Childhood onset; continuous traits of distractibility, restlessness, and irritability	Marked by high accomplishments, social gifts, and decreased need for sleep	10%
Cyclothymic temperament	Childhood onset; continuous problems with organization, attention, and distraction	Mood symptoms are more prominent than they are in ADHD	20%
True ADHD comorbidity	N/A	N/A	10%–20%

Sources: Torres I et al, Acta Psychiatr Scand *2015;132(5):389–399; Vöbringer PA et al,* J Affect Disord *2012;136(3):577–580*

The affective temperaments

Hypomanic symptoms are sometimes woven into the patient's temperament in ways that resemble ADHD. Compared to unipolar patients, patients with bipolar disorder have high levels of inattention, restlessness, and excessive daydreaming when they are not in an episode (Akiskal HS et al, *Arch Gen Psychiatry* 1995;52(2):114–123; Clark L et al, *Biol Psychiatry* 2005;57(2):183–187). Like ADHD, these traits have a childhood onset and a continuous course, making it very difficult to tease the two apart.

Temperamental differences have been recognized in bipolar patients for over 100 years, and they are generally clustered into four categories: dysthymic, hyperthymic, cyclothymic, and irritable. The affective temperaments that most resemble ADHD are the hyperthymic (ie, hypomanic traits) and cyclothymic (frequent alterations between hypomanic and depressive traits).

Hyperthymic patients often present because they lack patience and attention during tedious tasks. Like patients with ADHD, they are physically restless, become easily distracted, and tend to talk over others. What sets them apart from ADHD patients is their high level of accomplishment and decreased need for sleep. These patients are driven, and that drive has a focus that propels them to success in the working world, where they often rise to leadership positions.

The cyclothymic temperament is marked by unpredictable shifts from energized to sluggish, extroverted to withdrawn, passionate to disinterested. The result is inconsistent work performance, disorganization, and a lack of focus that can look just like ADHD. In theory, mood symptoms like lability, irritability, depression, and insomnia should distinguish this temperament from ADHD, but telling them apart is not so easy because these affective traits are also common in ADHD (Ozdemiroglu F et al, *Psychiatry Investig* 2018;15(3):266–271).

A quick way to learn about these temperaments is to read the TEMPS-A, a self-report questionnaire that captures the hallmark features of each type. This scale is the gold standard for evaluation of the affective temperaments and is available at www.psychiatryletter.net. Patients circle the statements on the questionnaire that apply to them. For cyclothymic, those include "I constantly switch between being lively and sluggish" and the ADHD-like "I often start things and then lose interest before finishing them." For hyperthymic, they include "I am totally comfortable even with people I hardly know" and the ADHD-like "I am always on the go."

Putting it all together

When an adult with bipolar disorder presents with ADHD-like symptoms, use the following steps to figure out the cause:

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Research Updates IN PSYCHIATRY

ACUTE MANIA

Brexpiprazole Ineffective in Mania

REVIEW OF: Vieta E et al, *J Psychopharmacol* 2021;35(8):971–982

TYPE OF STUDY: Phase III randomized controlled trials

Brexpiprazole is FDA approved in schizophrenia and as an adjunct for major depression and is one of the better-tolerated antipsychotics. Like aripiprazole, it is a partial D2 and 5-HT1A agonist. Unlike most antipsychotics, brexpiprazole has never been studied in acute mania, so these two recently published industry-sponsored trials give us the first glimpse of its antimanic potential.

The trials employed similar designs. Both were large, randomized, placebo-controlled trials that compared brexpiprazole with placebo over three weeks in acute bipolar I mania. The participants were drawn from US and European sites and had a Young Mania Rating Scale (YMRS) score over 24 at entry. Brexpiprazole was started at 2 mg/day and titrated up to 4 mg/day as tolerated. No other medication was allowed except lorazepam on an as-needed basis. The trials enrolled 654 patients, over 75% of whom completed the acute phase.

After three weeks, YMRS scores were about the same for drug and placebo, although the brexpiprazole group scored a little better on the secondary Clinical Global Impression—Bipolar Disorder (CGI-BD) measure.

Both trials included an open-label, long-term phase where symptoms were treated with brexpiprazole for another six months if the investigators thought patients would benefit from continued treatment. Outcome measures over the 26 weeks of this phase showed gradual decreases in YMRS and CGI-BD scores, but the changes were not dramatic and there was no control arm to compare them to.

Brexpiprazole was well tolerated, with akathisia the most commonly reported adverse effect. During the open-label extension, six patients became manic, five became depressed, and four developed suicidal ideation, but these events lacked a placebo arm for comparison.

The multicenter design may have obscured the drug-placebo difference. There are more investigators per patient in multicenter trials, increasing the attention each patient receives and amplifying the placebo effect. However, other antipsychotics have overcome this and yielded positive results in mania during multicenter trials.

The authors conducted a secondary analysis in an attempt to salvage some signal of response in these patients. Based on earlier evidence that poor insight predicts a better response to antipsychotics in mania (Welten CCM et al, *J Clin Psychopharmacol* 2016;36(1):71–76), they reanalyzed the data and found that poorer insight was associated with a statistically significant improvement on brexpiprazole relative to placebo (odds ratio 2.2, CI 1.1–4.4).

TCPR'S TAKE

The atypical antipsychotics are a varied class, and we can't conclude all of them work in acute mania. Stick with those that are FDA approved in mania (aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone), as the others in this class are either untested (eg, lumateperone, lurasidone) or have negative results in this condition (eg, paliperidone).

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

METABOLIC SYNDROME

Omega-3s and Metabolic Risks in Schizophrenia

REVIEW OF: Pawełczyk T et al, *Schizophr Res* 2021;230:61–68

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

Patients with schizophrenia are at greater risk for metabolic syndrome, whether from lifestyle, antipsychotic side effects, or the illness itself. Omega-3 fatty acids have metabolic benefits in the general population, and levels of these "healthy fats" tend to be low in people with schizophrenia. Earlier research found that omega-3 supplementation improved negative symptoms in schizophrenia, and this study examined their metabolic effects in schizophrenia.

This was a randomized, double-blind, placebo-controlled trial of 71 adults with stable schizophrenia on antipsychotic medication. They were treated with either omega-3 fatty acids or a fish-flavored placebo for six months. Both the placebo and the active intervention contained 0.2% alpha-tocopherol (vitamin E) to prevent oxidation of fatty acids. The omega-3 intervention consisted of a 3:1 ratio of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids with a total daily dosage of 2,200 mg/day. Body composition and metabolic parameters associated with metabolic syndrome were assessed at baseline, then at eight and 26 weeks after study initiation. Both groups began the trial with similar metabolic parameters.

After eight weeks, the placebo group had a nonsignificant increase in metabolic syndrome ($p = 0.083$), and this increase was even greater at 26 weeks ($p = 0.007$). By contrast, the rate of metabolic syndrome decreased in the treatment group, although the effect was just marginally significant ($p = 0.0408$). Notably, the omega-3 group had significant reductions in fasting blood glucose ($p = 0.045$), total cholesterol ($p = 0.037$), and blood glucose levels ($p = 0.034$), but improvements in other metabolic parameters were not significant. Patients on olanzapine experienced the greatest metabolic benefits with omega-3s.

The investigators also found an association between triglyceride level and the psychopathology subscale of the Positive and Negative Syndrome Scale, suggesting that lower triglycerides are associated with improved symptoms of psychopathology ($p = 0.0008$).

Omega-3s were well tolerated in this study. They have a mild anticoagulant effect, but patients on anticoagulants may still be able to take omega-3s with approval from their prescribing physician. Omega-3 supplementation may deplete vitamin E, which notably was supplemented in this study.

The 3:1 EPA:DHA ratio used in this study can be difficult to find but is worth the search, as this is also the ratio that

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CME Post-Test

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

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

1. Light therapy for insomnia improved what outcomes in older adults with cognitive impairments, dementia, or Parkinson's disease (LO #1)?
   - [ ] a. Memory and attention
   - [ ] b. Energy and memory
   - [ ] c. Mood, behavioral disturbances, and sleep
   - [ ] d. Mood disturbances, cognition, and quality of life
2. Patients with a hyperthymic temperament have what characteristic(s) distinguishing them from patients with ADHD (LO #2)?
   - [ ] a. Physical restlessness
   - [ ] b. Irritability and unpredictable shifts from passionate to disinterested
   - [ ] c. Depression and the tendency to talk over others
   - [ ] d. A high level of accomplishment and a decreased need for sleep
3. Which treatment has been shown to improve OCD in schizophrenia and schizoaffective disorder (LO #3)?
   - [ ] a. Mirtazapine
   - [ ] b. Lamotrigine
   - [ ] c. Clozapine > 300 mg/day
   - [ ] d. Pramipexole
4. After three weeks in recent trials, how did brexpiprazole compare to placebo on the primary outcome, Young Mania Rating Scale (YMRS) in bipolar mania (LO #4)?
   - [ ] a. Brexpiprazole significantly outperformed placebo
   - [ ] b. Placebo significantly outperformed bexpiprazole
   - [ ] c. Brexpiprazole did not separate from placebo significantly
   - [ ] d. Brexpiprazole significantly outperformed placebo, but the result was compromised by a high dropout rate
5. In a recent study, light therapy reduced the core symptoms of combat-related PTSD; however, benefits in PTSD were unrelated to sleep or circadian rhythm changes (LO #1).
   - [ ] a. True
   - [ ] b. False

How to Diagnose ADHD in Bipolar Disorder

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1. Wait until their mood episodes have resolved for 4–6 months before assessing for ADHD.
2. Assess for childhood onset of ADHD before age 12 to rule out cognitive deficits from the progression of bipolar disorder.
3. Rule out other causes of cognitive problems like substance use, sleep deprivation, traumatic brain injury, and medical illnesses (eg, sleep apnea, hypothyroidism, cerebrovascular disease, recent infection).
4. Look for signs of lifelong affective temperaments that might better explain the symptoms.
5. Carefully assess for ADHD with the DSM-5 criteria, preferably using a structured interview.

A structured interview will help filter out some of the symptomatic mimicry that confuses the picture. It sounds cumbersome, but it's not. These instruments simply translate the DSM criteria into questions like "Do you often have difficulty sustaining your attention in tasks? And how was that in your childhood?" The DIVA-5 is a good option for ADHD (www.divacenter.eu, $12 one-time fee). Two others covering a wider array of psychiatric disorders are the MINI-7.0 (www.harm-research.org, $10 plus a per-use fee) and Abraham Nussbaum's *Pocket Guide to the DSM-5 Diagnostic Exam* (Arlington, VA: American Psychiatric Publishing; 2013).

Those steps do a pretty good job of ruling out other causes of ADHD, but one problem remains. What if your patient meets the full DSM-5 criteria for ADHD and also has a prominent affective temperament? We don't have a good way to tease those apart, so it's best to proceed gingerly with treatment, starting with medications for ADHD that have a low risk of causing mania (eg, clonidine or guanfacine). I'll get into that more in a future article on treating ADHD in patients with bipolar disorder.

TCPR VERDICT: Cognitive symptoms are common in bipolar disorder, even after the mood episodes have resolved. Common causes include cognitive deficits from the progression of mood episodes, affective temperaments like cyclothymic or hyperthymic, or a genuine comorbidity with ADHD. A detailed history and some structured testing can clarify the cause.

For a guide to nonpharmcologic ways to improve cognition, search for "Pocket Psychiatrist" (our patient edition) on your podcast store and scroll to the 5/3/21 episode.

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Light Therapy: Good for What Ails You?

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trial in type II diabetes (Brouwer A et al, *Diabetes Care* 2019; 42(4):529–538).

TCPR VERDICT: Light therapy improves sleep and circadian rhythms and is a first-line treatment for seasonal affective disorder. It is worth considering for nonseasonal depression, antidepressant augmentation, bipolar depression, and depression in traumatic brain injury. It may also improve PTSD, ADHD, bulimia, and sexual dysfunction in men, but here it is best reserved for patients who prefer natural treatments or do not tolerate conventional ones.

To learn more, listen to our 7/26/21 podcast, "How to Use a Light Box." Search for "Carlat" on your podcast store.

Research Updates

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worked in studies of depression. We found three products with a similar ratio that were tested by independent labs: Viva Naturals (on Amazon), Member's Mark (at Sam's Club), and Kirkland Signature (at Costco) at a cost of 15–25 cents/day.

TCPR'S TAKE

This study is small and preliminary, but omega-3s have established benefits for metabolic health in various conditions and are worth considering in schizophrenia.

—Batya Swift Yasgur, MA, LSW, and Chris Aiken, MD. The authors have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.