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Chris Aiken, MD
Editor-in-Chief

Volume 19, Issue 11 & 12
November/December 2021
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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. Differentiate bipolar disorder from other conditions that have some symptomatic overlap with hypomania.
2. Identify the pros and cons of the FDA's approval of aducanumab in its current form for the treatment of early Alzheimer's disease and mild cognitive impairment.
3. Incorporate nutritional psychiatric theory into clinical practice.
4. Summarize some of the current research findings on psychiatric treatment.

How to Treat 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.

Patients with bipolar disorder often present with cognitive complaints. Our October 2021 issue laid out a diagnostic plan for these symptoms, and in this article, I'll cover some treatment approaches for patients with a DSM-based ADHD-bipolar comorbidity (ie, the ADHD symptoms began in childhood and persist after the mood episodes have stabilized).

Stimulants in bipolar disorder

Stimulants are the mainstay treatment in ADHD, but they carry several risks that are pertinent to bipolar disorder: mania, psychosis, insomnia, substance abuse, and neurotoxicity. Overt mania is rare on them, and mood stabilizers lower that risk significantly—however, lamotrigine, which is not anti-manic, doesn't

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Highlights From This Issue

Dr. Gordon Parker describes how to tell the difference between hypomania and normal happiness.

Clonidine and guanfacine are among the safer options for the bipolar-ADHD overlap, but if you have to use a stimulant, there are reasons to choose methylphenidate over amphetamine.

Nutritional psychiatry has three RCTs supporting its benefits in depression, and Dr. Drew Ramsey shares simple ways to weave these ideas into practice.

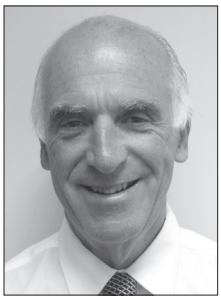
A review of two new FDA approvals: viloxazine (Qelbree) in ADHD and aducanumab (Aduhelm) in dementia.

Q&A With the Expert

How to Diagnose Bipolar Disorder
Gordon Parker, MD, PhD, DSc

Scientia Professor of psychiatry at the University of New South Wales. In 2002 he founded the Black Dog Institute, a clinical research center for mood disorders. Dr. Parker's research has focused on the phenomenology and diagnosis of depression and bipolar disorder.

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



TCPR: When I ask a depressed patient if they've ever had manic symptoms, I often run into a problem. They say, "Of course I feel more confident, energetic, and happy ... *when I'm not depressed.*"

Dr. Parker: As it can be hard to tease apart true hypomania from normal happiness, we've developed a rating scale to assist, the Sydney Bipolar Screener. We evaluated 94 symptoms of mania and hypomania in patients who were already diagnosed with bipolar or unipolar disorder. We asked the patients with bipolar disorder to check the items that reflected their "highs," and the unipolar patients to check the items that described times when they were "happy." We used a machine learning strategy to filter out the items that overlapped with normal happiness. In the end, that whittled the set down to 10 symptoms that separated bipolar from unipolar with a high predictive accuracy—over 90% (Parker G et al, *J Affect Disord*

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Expert Interview—How to Diagnose Bipolar Disorder
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2021;281:505–509). (*Editor's note: See The Sydney Bipolar Screener table on page 4.)*

TCPR: What is the main thing that separates out the bipolars?

Dr. Parker: Energy. The most distinguishing item was "I have very high levels of energy." Items related to euphoria and heightened emotions didn't make the cut. One item that didn't make the top 10 but that we do see a lot in mania and hypomania is decreased need for sleep. I think the key issue is not just asking "Do you need less sleep?" but extending the question by saying "Do you sleep less and find that you're not tired the next day?"

TCPR: What's your top screening question for bipolar disorder?

Dr. Parker: The first screening question I use in my clinical assessment is, "Apart from the times when you're depressed and when your mood is normal, do you have periods when you're energized and wired?" This puts energy front and center. Energy was not part of the core "Criterion A" definition of mania in DSM-IV, but they brought it in for DSM-5, which I think was wise.

TCPR: You're leading a task force that is proposing changes to DSM criteria for mania and hypomania. How would you change the core definition: "A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently goal-directed behavior or energy"?

Dr. Parker: We have a minor tweak for that one. We'd emphasize that the elevated mood is not just happiness but is an "overshoot." Thus: "A distinct period of abnormal and persistently elevated, expansive, or irritable mood, with the individual feeling energized and 'wired,' and which is perceived as an 'overshoot' and not simply a state of happiness, and generally oscillating with periods of depression."

TCPR: You also added a part about cycling with depression.

Dr. Parker: That can help reduce false positives. I think it's very rare for people to only have hypomanic or manic episodes without depressions. In my experience, I've seen maybe three or four people like that over my lifetime.

TCPR: Are bipolar depressions different from unipolar depressions?

Dr. Parker: Bipolar depression is more likely to be melancholic, and possibly psychotic. When I say "melancholic," I'm not referring to the DSM criteria for melancholic features. I'm speaking more generally of a severe depressed state where their mood is nonreactive, they have anhedonia, a distinct lack of energy, foggy concentration, and maybe other psychomotor changes. So when I want to establish a diagnosis of bipolar disorder, I look for manic features but I also check out the nature of their depressions.

TCPR: What else would you change in the DSM criteria for bipolar?

Dr. Parker: Another problem is how the DSM separates mania from hypomania. First, the use of the same list of symptoms for both states is problematic. To separate them, the DSM uses severity (mania causes significant impairment), duration (hypomania is at least four days while mania is at least seven days), and hospitalization and psychotic features (these last two automatically shift the diagnosis to mania). I don't know of any other medical condition where hospitalization is a criterion. It depends too much on external variables like social supports and the health care system.

TCPR: What about duration?

Dr. Parker: The problem there is that the four- and seven-day cutoffs the DSM uses for hypomania and mania have never been empirically validated. Patients who meet the full duration criterion have the same clinical features as those whose elevated moods are classic and recurrent, but shorter in duration (Parker G and Fletcher K, *J Affect Disord* 2014;152–154:57–64). Even when patients meet the full duration criterion, their typical episodes tend to be shorter. For 60% of patients with bipolar II, the average episode of hypomania lasts fewer than four days, and for 40% of patients with bipolar I, the average mania lasts fewer than seven days. In practice, when you ask a patient how long their episodes last, their answer is likely to reflect their typical episode, which means you'll miss a lot of people with true bipolar disorder by applying the DSM-5 duration criterion.

TCPR: A lot of papers have argued for reducing the duration, particularly with hypomania. Why has DSM stuck with it?

Dr. Parker: I think they're being conservative and trying to respect concerns about overdiagnosis, but I think those concerns can be addressed by more precise definitional criteria rather than by a "safety" duration period.

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Mailing Information

The Carlat Psychiatry Report (ISSN 2473-4128) is published monthly, excluding July and Dec., by Carlat Publishing, LLC; 2 Prince Place, Newburyport, MA 01950. Periodicals Postage Paid at Newburyport, MA and at additional mailing offices.

POSTMASTER: Send address changes to *The Carlat Psychiatry Report*, P.O. Box 626, Newburyport, MA 01950.

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Technically DSM-5 does recognize the short-duration cases with "depressive episodes with short-duration hypomania," but that's in the back of the book as a "condition for further study."

TCPR: What separates mania from hypomania in your view?

Dr. Parker: For me, it is the presence of psychotic features. If you have psychosis during an elevated state, it's bipolar I. If you don't, then it's bipolar II.

TCPR: Do you mean delusions and hallucinations, or do you take a broader view of psychosis, including distorted thinking and thought-blocking?

Dr. Parker: I'm speaking just of delusions and hallucinations. These aren't always easy to diagnose, as there is a fine line between a delusion and an overvalued idea. For example, the average patient becomes grandiose during a high. They think they're going to be the boss of the company or write the great Australian novel. To diagnose psychosis, I look for pretty black-and-white features such as, "When I'm high, I have a voice in my head telling me I am God." I'm looking for distinctive and clear-cut psychotic delusions or hallucinations.

TCPR: There is also a fine line between heightened sensations and hallucinations.

Dr. Parker: Yes, and that's important to recognize because patients with both bipolar I and bipolar II tend to have highly sensitive perceptions, but I would not classify those as hallucinations (Parker G et al, *Australas Psychiatry* 2018;26(4):384–387). I have patients that will say, "I can hear a car in the street three blocks away" and I can't hear anything. Smells are more powerful. One patient stepped on some dog poo while in an elevated mood—they wiped it off, but they could smell it for the whole day. Sometimes these sensations are a source of creativity. One patient told me when she's listening to an orchestra, she has the capacity to bring out and separate every instrument and then rejoin them together.

"If you have psychosis during an elevated state, it's bipolar I. If you don't, then it's bipolar II. There is a fine line between a delusion or hallucination and an overvalued idea. To diagnose psychosis, I look for black-and-white features such as, 'When I'm high, I have a voice in my head telling me I am God.'"

Gordon Parker, MD, PhD, DSc

TCPR: Does a patient's judgment tell you about possible delusional thinking? For example, suppose a patient with bipolar disorder tells you they've taken out all their retirement savings to start a chain of ice cream stores. They teach elementary school and have no business experience. That's out of touch with reality, but is it delusional?

Dr. Parker: I would strongly consider psychosis in that case because it suggests delusional confidence. On the other hand, if a multimillionaire took out $200,000 to start a new business, I'd be less inclined to think it was delusional. Mania and hypomania also tend to differ in how the patient recalls the episode. After the episode, the hypomanic patient is likely to feel great shame about what they did while the manic patient may not remember it or be inclined to deny it.

TCPR: One way the DSM separates mania from hypomania is by the level of impairment. What's wrong with that definition?

Dr. Parker: The DSM wording is imprecise: "marked impairment" for mania and "not severe enough to cause marked impairment" in hypomania. How are clinicians meant to judge the difference? Further, it puts the weight on impairment, when in reality there's a significant percentage of patients with mania and hypomania who say their functioning is distinctly improved, and they may well be right if creativity or productivity is the benchmark for functioning.

TCPR: Getting back to hypomania vs normal happiness, is there a clear, categorical line between them, or are they on a continuum?

Dr. Parker: Our studies support a categorical view. When we plot the answers to a bipolar screening measure, we observe a bimodal distribution, so there is a clear separation between normal elevated mood and the hypomania of bipolar disorder. And when we throw in bipolar I patients we get a trimodal distribution, so there is a categorical separation between hypomania and mania as well (Parker G et al, *Psychiatry Res* 2021;297:113719).

TCPR: Sometimes it doesn't seem so clear cut in practice.

Dr. Parker: In clinical practice, about 2% or 3% of patients who present for evaluation of bipolar have hypomanias that are so mild that I'm not entirely sure that they've truly got bipolar disorder, but it's a very, very small minority. If you go through the diagnostic steps, you can usually identify the patients with true bipolar disorder.

TCPR: What are those steps?

Dr. Parker: Start with a screening question, like the one I suggested about energy. If they say "no" or are unsure, double-check by asking, "You *don't* have times when you are more energized, elated, and overconfident, in a way that is distinct from your normal self?" If one of those tries is a "yes," move forward and check for the rest of the DSM symptoms of hypomania/mania. Ideally, you want to identify clear and unequivocal episodes of hypomania or mania. Then ask about the depressive phases. Are the depressions recurrent and cyclical? Do at least some of them have melancholic features in the way I described? Next, I would look for a family history. Patients with true bipolar disorder will almost invariably report a family history of either depression or bipolar in their first- or second-degree relatives. About half will report bipolar in their family, but

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the other half will usually report depression (Suppes T et al, *J Affect Disord* 2001;67(1–3):45–59).

TCPR: Anything else?

Dr. Parker: Finally, age of onset can also be helpful, as most bipolar disorder starts in adolescence, particularly between ages 15 and 20. Age of onset is a strong indicator, and it can help to differentiate bipolar disorder from other conditions that share some symptomatic overlap with hypomania, like ADHD and borderline personality disorder. Those two disorders tend to start much earlier. (*Editor's note: Borderline personality disorder cannot be diagnosed until age 18, but adults with this disorder can usually trace some of their symptoms back to early childhood.)*

TCPR: If the patient checks all those boxes, are you pretty sure they have bipolar disorder?

Dr. Parker: Yes, and I'll tell them that. I always apologize first and say, "This is going to sound a bit arrogant, but I believe with a 100% level of confidence that you've got (say) bipolar II." Or if I'm not 100% confident, I'll say so and explain why. It may be that they don't check all the boxes, or there are other things going on like substance use that might explain the symptoms. And then I'll detail what needs to be done to obtain a firmer diagnosis.

TCPR: You're very direct about it. How do patients respond?

Dr. Parker: They seem to appreciate a firm diagnosis as it allows them to get on with their lives. They now know what they've got and they can go on Google and read about it. And, of course, you hope to find the right medication and they'll have it all come under control. I believe that most people with a bipolar condition do well when we find right medication.

TCPR: The right medication may be different for everyone, but what are the go-to meds that you often start with?

Dr. Parker: My preferred drugs are lithium for bipolar I and lamotrigine for bipolar II.

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

The Sydney Bipolar Screener

Apart from times when you are depressed or in a normal mood state, do you have times when you feel "up"? If so, check whether you experience any of the following features.

I have very high levels of energy	❑ Yes ❑ No
I feel "bulletproof" or invulnerable	❑ Yes ❑ No
I talk over people and am difficult to interrupt	❑ Yes ❑ No
My thoughts race so quickly that it is difficult to retain them	❑ Yes ❑ No
I am irritable and angry	❑ Yes ❑ No
My judgment becomes impaired	❑ Yes ❑ No
I am much more creative	❑ Yes ❑ No
I am very distractible	❑ Yes ❑ No
I feel that I can achieve great things	❑ Yes ❑ No
I talk more quickly	❑ Yes ❑ No

Score 1 point for each item endorsed. For patients with a history of depression, a score of 6 or more suggests a strong likelihood of bipolar disorder (97% sensitivity and 96% specificity).

Stay tuned for our podcast, "A New Way to Diagnose Bipolar: An Interview With Gordon Parker." Search for "Carlat" on your podcast store.

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How to Treat ADHD in Bipolar Disorder

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count here (Viktorin A et al, *Am J Psychiatry* 2017;174(4):341–348). More common is milder symptomatic worsening. Around one in seven patients with bipolar disorder and ADHD experienced worsening of mood, irritability, or anxiety on stimulants—even with mood stabilizers in place, based on results from six small clinical trials.

These risks may be a little less pronounced with methylphenidate than the amphetamines (eg, Adderall, Dexedrine, Vyvanse). Amphetamine has been used as an animal model of mania since 1978, and it is twice as likely to trigger psychosis than methylphenidate (Moran LV et al, *N Engl J Med* 2019;380(12):1128–1138). Methylphenidate, in contrast, was once thought to treat mania by stabilizing mental arousal, and although this theory did not pan out in a recent trial in acute mania, methylphenidate at least did not worsen mania in that brief, three-day, placebo-controlled trial (Hegerl U et al, *Eur Neuropsychopharmacol* 2018;28(1):185–194). Methylphenidate also has a lower abuse potential, judging from its rewarding properties in preclinical studies. Finally, amphetamine has more neurotoxic properties than methylphenidate, such as depleting vesicular pools of dopamine (Moratalla R et al, *Prog Neurobiol* 2017;155:149–170, although this problem has only been documented in animal studies using high doses—eg, equivalent to amphetamine 140–700 mg/day in humans).

What about the benefits of stimulants in this population? Only three placebo-controlled trials looked at ADHD symptoms in patients with stable bipolar disorder, two of which were positive. These studies, which were conducted in children, were limited in size (total n = 63), duration (two weeks), and design (crossover instead of parallel group) (Zeni CP et al, *J Child Adolesc Psychopharmacol* 2009;19(5):553–561).

The bottom line is that stimulants pose risks in bipolar disorder, so we'd be better off with safer alternatives when possible.

Nonstimulant options

My top choices for ADHD in bipolar disorder are the alpha-agonists (clonidine [Kapvay] and guanfacine [Intuniv]) and the modafinils (armodafinil [Nuvigil] and modafinil [Provigil]). The alpha-agonists are FDA approved in pediatric ADHD

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and improve executive functioning in various populations, including schizophrenia, substance use disorders, and ADHD (Arnsten AFT, *Neurobiol Learn Mem* 2020;176:107327). Modafinil came close to FDA approval in ADHD but was held back when a child developed Stevens-Johnson syndrome on the drug (a rare but real risk). Compared to the stimulants, these two classes of medications have smaller effects in ADHD, but they also have broader benefits in bipolar disorder.

The modafinils have been effective for bipolar depression in some, but not all, trials. The negative findings may result from the fact that they improve only energy, alertness, and attention, rather than the full depressive syndrome (see *TCPR* June/July 2020). The alpha-agonists, particularly clonidine, improve sleep, irritability, and anxiety in various populations. Neither of these nonstimulant options are neurotoxic, and the modafinils have neuroprotective effects, increasing synaptic plasticity in the hippocampus (Yan YD et al, *Transl Psychiatry* 2021;11(1):116). Regarding manic risk, the alpha-agonists did not cause or worsen mania in clinical trials, while the modafinils have both caused and treated mania in case reports (Hardy-Bayle MC, *Encephale* 1989;15(6):523–526; Schoenknecht P et al, *Biol Psychiatry* 2010;67(11):e55–e57).

Atomoxetine, viloxazine, and ... lithium?

Although approved in ADHD, atomoxetine (Strattera) and viloxazine (Qelbree) are controversial in bipolar disorder because these antidepressant-like compounds can induce mania (Perugi G and Vannucchi G, *Expert Opin Pharmacother* 2015;16(14):2193–2204). Stimulants are usually better options than these, as their manic risk is at least balanced by a more substantial benefit in ADHD.

Surprisingly, lithium has a controlled study in adult ADHD *without* bipolar disorder where it worked as well as methylphenidate 40 mg/day on measures of ADHD, mood, and irritability (lithium levels were 0.5–0.7).

Treatments for ADHD in Bipolar Disorder

Medication	Dosage	Notes
Clonidine and guanfacine	ER: 0.1–0.4 mg/day.[1] IR: 0.1–0.3 mg/day. Transdermal (clonidine only): 0.1–0.3 mg/day weekly patch.	Start with ER, which is FDA approved for ADHD and generic. Start QHS and divide BID at higher doses. The weekly clonidine patch improves on tolerability. Taper off gradually to avoid rebound hypertension.
Modafinils	Modafinil: 100–200 mg/day. Armodafinil: 150–250 mg/day.	Armodafinil has a longer duration and steadier effects than modafinil. Find low-cost options at goodrx.com if not covered by insurance.
Omega-3s	EPA + DHA = 1000–3000 mg/day, with EPA ≥ 2 times DHA amount.	Reliable brands include Viva Naturals (Amazon), Member's Mark (Sam's Club), and Kirkland (Costco) (15–25 cents/day).
Stimulants	Prefer methylphenidate over amphetamines. Start with methylphenidate ER 18 mg/day.	Use lowest effective dose. If tolerance develops, revisit the diagnosis before raising it further.
Lifestyle	Aerobic exercise, Mediterranean diet, good sleep, and mindfulness improve both ADHD and mood disorders.	

[1]Only 75% of the ER is absorbed, so the IR and patch have lower dose ranges

Omega-3s

For patients who prefer a non-medication approach, omega-3 fatty acids are a good place to start. This supplement improved bipolar depression and emotional and cognitive symptoms of childhood ADHD with a small effect size, according to meta-analyses of seven to eight placebo-controlled trials in each disorder (Kishi T et al, *Bipolar Disord* 2021 (Epub ahead of print); Chang JP et al, *Neuropsychopharmacology* 2018;43(3):534–545). Notably, omega-3s tended to work better in the ADHD studies when the dose was brought closer to the range used in the bipolar trials. (See the Treatments for ADHD in Bipolar Disorder table above.)

Practical pearls for treating bipolar plus ADHD

I usually start with an alpha-agonist if the patient has insomnia, or the modafinils if they struggle more with depression and fatigue. Of the two alpha-agonists, guanfacine has more evidence to improve executive functioning, while clonidine has more studies in related comorbidities like self-harm, PTSD, and opioid and nicotine use disorders. Clonidine is also more sedating. Among the modafinils, most patients prefer armodafinil for its steadier plasma levels and longer duration of action.

The alpha-agonists take a few weeks to work in ADHD, while the modafinils have same-day effects much like the stimulants. With traditional stimulants, assessing response is tricky because their rewarding effects may bias the patient's report. In my experience, the following signs point to a true ADHD response:

- *Calming:* Improvement in hyperactivity, impatience, and irritability
- *Executive function:* Better able to organize and prioritize complex tasks
- *Sustained improvement*

In contrast, patients without ADHD usually emphasize benefits in energy and motivation and may have "crashing fatigue" as the stimulant wears off at the end of the day. After a few months, tolerance tends to develop, prompting requests for higher and higher doses.

TCPR VERDICT: About 10%–20% of patients with bipolar disorder have DSM-based ADHD. To treat this comorbidity, stabilize mood first. Alpha-agonists and the modafinils are good options to start with, while the stimulants may carry risks in bipolar disorder, particularly the amphetamines.

In the News: Aducanumab (Aduhelm)

Rehan Aziz, MD. Associate professor of psychiatry and neurology, Rutgers Robert Wood Johnson Medical School.

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

Alzheimer's disease (AD) is devastating. There is no cure and existing treatments don't slow or stop its progression. In June 2021, the FDA approved aducanumab (pronounced a-due-KAN-you-mab, brand name Aduhelm) for the treatment of AD. It's the first new AD med since 2003 and is the only treatment that directly attacks a component of AD's purported underlying pathology. The approval has brought hope to those dealing with the illness, but the FDA's decision has also been controversial.

What are the indications? How does it work?

Initially, aducanumab was approved for all stages of AD, but the FDA updated its endorsement in July. Aducanumab is now recommended only for mild cognitive impairment (MCI) and mild AD, which is the population in which it was originally studied.

Aducanumab is an intravenous (IV) antibody infusion. It targets and helps to break down clumps of beta-amyloid in the brain. Beta-amyloid, along with pathological tau, are the two problem proteins found in AD. Unfortunately, the role of beta-amyloid in AD is unclear, and multiple trials of other drugs that do the same thing have already failed.

Does it work?

The efficacy of aducanumab was evaluated in two double-blind trials, totaling 3285 patients with either MCI or mild AD. Patients were randomized to receive low-dose (3 or 6 mg/kg) aducanumab, high-dose (10 mg/kg) aducanumab, or placebo IV every four weeks for 18 months. The primary endpoint was slowing of cognitive decline and functional impairment with aducanumab compared to placebo. This was evaluated by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score. This scale measures memory; orientation; judgment and problem solving; and functioning in the community, at home, in hobbies, and in personal care. The manufacturer stopped both trials early after a preliminary analysis concluded that the drug was not more effective than placebo. However, in both studies, aducanumab significantly reduced beta-amyloid deposits in the brain (Aducanumab (Aduhelm) for Alzheimer's Disease, *Med Lett Drugs Ther* 2021;63(1628):105–106).

Controversy erupted when the manufacturer later reanalyzed a portion of the data and found that in one trial, but not the other, the highest dose of aducanumab was associated with reduced clinical decline compared to placebo in the CDR-SB score and other tests of cognitive function. This occurred only in the last week, week 78. The reduction was statistically significant, though the actual difference was small and of uncertain real-life significance (Biogen, Aduhelm prescribing information, revised 6/2021).

Rather than conduct a new study with this subgroup, the company applied for FDA approval. Critics have argued that cherry-picking the data after the study was stopped early does not pass scientific rigor and is not statistically valid (Alexander GC et al, *JAMA* 2021;325(17):1717–1718).

Why was it approved?

Technically, aducanumab isn't fully approved. It was accepted under the FDA's accelerated approval pathway. This track is used for medications targeting serious or life-threatening illnesses that *may* provide therapeutic benefit over existing treatments. To qualify, a drug must show that it changes the biology of the disease in a way thought to likely benefit patients. If post-marketing data show that the drug provides clinical benefit, then the FDA will grant traditional approval for the drug. If the data are negative, the FDA could remove it from the market.

What are the side effects?

Aducanumab causes amyloid-related imaging abnormalities (ARIAs). These are visible on MRIs and fall into two categories: 1) brain swelling and 2) small brain bleeds. Because of this, people taking blood thinners or who are otherwise prone to bleeding should avoid taking aducanumab.

ARIAs can occur at any time during treatment and are fairly common. Thus, patients on aducanumab require frequent brain MRIs to monitor for ARIAs. At the treating dose, brain edema occurred in 35% of patients (vs 3% on placebo) and microhemorrhages in 21% (vs 1% on placebo). About one in four patients with ARIAs had clinical symptoms associated with them, including headache (13%), confusion (5%), dizziness/vertigo (4%), visual disturbance (2%), and nausea (2%). Most of these symptoms (88%) were self-resolving and only 0.3% fell in the serious range, although the long-term impact of ARIAs is unknown.

Other common adverse reactions were falls (15%) and diarrhea (9%), and according to the Aduhelm prescribing information one patient developed signs of an allergic reaction (angioedema and urticaria).

How is it given? How expensive is it?

Aducanumab is administered as an IV infusion given over one hour every four weeks. The medication is titrated gradually over six months toward a target dose of 10 mg/kg. Most patients require chronic treatment for dementia, although the studies only stretched out to 78 weeks. A brain MRI should be obtained before starting treatment and before the seventh and twelfth infusions to monitor for adverse events.

Aducanumab is priced at $56,000 annually for the drug alone, excluding costs from doctor visits, associated imaging, or administration at infusion centers. Several private insurers have already declined to cover it and several hospital systems won't offer it, arguing that the cost/risk does not outweigh its tenuously proven benefit. Medicare and Medicaid are reviewing their coverage decisions.

TCPR VERDICT: Aducanumab has unclear evidence of benefit, and it can cause brain swelling and bleeding. To date, just over a hundred patients have received it. There are significant barriers to prescribing it, including high cost, side effect monitoring, obtaining insurance coverage, and arranging for its administration in infusion centers. For now, aducanumab isn't ready for prime time.

To learn more, listen to our podcast, "What's Wrong With How We Treat Dementia?" Search for "Carlat" on your podcast store.

Q&A With the Expert

Nutritional Psychiatry in Practice
Drew Ramsey, MD

Assistant clinical professor of psychiatry at Columbia University, founder of the Brain Food Clinic, and the author of four books on nutrition and mental health, including 2021's Eat to Beat Depression and Anxiety *(HarperWave).*

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

TCPR: Why should we talk about diet with our patients?

Dr. Ramsey: I am an avid practitioner of psychotherapy and psychopharmacology, but we often need more tools to help our patients, and there is a lot of science behind nutritional psychiatry. There are now three randomized trials showing that people with depression can benefit by shifting to a Mediterranean-style diet. In the SMILES trial, 32% of patients achieved full remission after changing their diet, compared to 8% of controls (Jacka FN et al, *BMC Med* 2017;15(1):23). Food is also a way to engage patients, and it puts us in the business of preventative mental health.

TCPR: Depression tends to improve when patients take on a new challenge. How did these studies control for that?

Dr. Ramsey: The trials used controls that have modest antidepressant effects on their own. In the SMILES trial, the control was a nondirective, supportive "befriending" therapy. That trial also looked at whether changes in weight, exercise, smoking, or self-efficacy predicted the improvements in depression, and they did not. The HELFIMED trial delivered the nutritional intervention in a group format, and the control was an activities group that played games and planned outings together (Parletta N et al, *Nutr Neurosci* 2019;22(7):474–487). There is also a negative study on whether nutritional counseling and/or a multinutrient supplement could prevent depression better than placebo in obese patients (Bot M, *JAMA* 2019;321(9):858–868).

TCPR: Are there other disorders besides depression where nutritional psychiatry is making headway?

Dr. Ramsey: There's some evidence from the SMILES trial that the Mediterranean-style diet improves anxiety, and that's something I've seen in my own practice. Also, we've seen some evidence in ADHD. A recent trial looked at the DASH diet (a diet for hypertension that is similar to the Mediterranean approach) in childhood ADHD. The children were not taking any stimulants, and their ADHD symptoms improved after four months with the diet. The placebo was a nonspecific dietary intervention that guided them to eat a certain amount of protein, fat, and carbohydrates (Khoshbakht Y et al, *Eur J Nutr* 2021;60(7):3647–3658).

> **"Data on nutritional interventions are largely focused on depression, but nutritional psychiatry is useful to patients struggling with a number of disorders, including anxiety, addiction, and even psychosis."**
>
> Drew Ramsey, MD

TCPR: What goes into the Mediterranean diet?

Dr. Ramsey: The changes don't have to be grand. In the SMILES trial, participants ate one more seafood meal a week, an extra half-serving of fruit a day, an extra serving of vegetables a day, and a couple more servings of beans a week. They ate more nuts, olive oil, and whole grains. The bigger change was in what they dropped, each week eating 21 fewer meals of highly processed foods, like fried, sugary, or "fast" foods and simple carbs.

TCPR: Do you have to be a nutritionist to do this work?

Dr. Ramsey: All mental health clinicians can make use of this. I've seen positive results in my own practice, where we run a training program in nutritional psychiatry, and you can see it in the research. One trial just used a 13-minute video on the Mediterranean diet followed by two five-minute phone calls, and even this minimal level of human contact was enough to reduce depression (Francis HM et al, *PLoS One* 2019;14(10):e0222768).

TCPR: What are some easy ways for patients to start this work?

Dr. Ramsey: One of my most common prescriptions is raw, unsalted nuts. People worry that nuts are calorically dense, and they are filling, but they are also packed with nutrients—full of fiber, protein, minerals, healthy fats, and slow-burning carbohydrates. *(Editor's note: See the Brain-Friendly Food Swaps table on page 8 for more ideas.)* Also look for foods they can get rid of, like simple sugars, sodas, and processed foods. And be careful about diet sodas and artificial sweeteners. Those just lead people to crave more sweet stuff, and they are associated with higher rates of depression and—in animals—hippocampal damage (Guo X et al, *PLoS One* 2014;9(4):e94715). I'd also get rid of all low-fat products, sugary breakfast cereals, and fried foods. If you have fried food, pan-fry at lower heat and use extra virgin olive oil (EVOO) or avocado oil.

TCPR: Why those oils?

Dr. Ramsey: EVOO is mostly a monounsaturated healthy fat, with phytonutrients that have antioxidant properties. Avocado oil is also good, but EVOO is less expensive and has more robust data. EVOO was included in the studies I've mentioned, and it also lowered depression on its own in a new trial that randomized people with depression to use 1.5–2 tablespoons per day of either EVOO or sunflower oil in their diet (Foshati S et al, *J Acad Nutr Diet* 2021; Epub ahead of print).

TCPR: What are "processed foods"?

Dr. Ramsey: Technically, any food that has been cooked, dried, or modified from its original form is processed. But what we're concerned with are *ultra-processed foods.* These tend to involve technologies that weren't available 100 years ago. (*Editor's note: See the Ultra-Processed Foods table on page 8.)* They are high in calories, low in nutrients, and have flavor

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Expert Interview—Nutritional Psychiatry in Practice
Continued from page 7

and texture enhancers that make people want to eat more and more.

TCPR: What type of patient would benefit most from nutritional interventions?

Dr. Ramsey: The data are largely focused on depression, but nutritional psychiatry is useful to patients struggling with anxiety, addiction, and even psychosis. Patients who are interested in nutrition are often more motivated, but the biggest impact is likely for those who are totally disengaged from food. One misconception is that nutritional psychiatry is only for patients with mild disorders. In the HELFIMED trial, 86% had severe depression.

TCPR: How directive are you with patients?

Dr. Ramsey: I try to be neutral and respect patient autonomy and individuality. We are all unique in our tastes, preferences, and morals about food, so I find it best to recommend broad categories. Thus my mantra these days is: "Seafood, greens, nuts and beans, and a little dark chocolate." That is a good start. We also focus on restoring a joyful relationship with food.

TCPR: Does depression get in the way of this work?

Dr. Ramsey: Yes, particularly problems with motivation, organization, and executive functioning—and also guilt. It can be overwhelming to think every meal is going to affect your mental health, and we don't want this food work to be another burden. Too much focus on food can derail other aspects of treatment. Skills and finances can also get in the way. Not everybody knows how to cook seafood or can afford fresh fish. Still, this work can be done on a low budget. In the SMILES trial, this diet actually lowered participants' food costs by more than $100 per month.

TCPR: Have there been further refinements beyond the Mediterranean approach?

Dr. Ramsey: Research is focusing on fermented foods, which improve the health and diversity of the gut microbiome. There are dozens of studies that associate poor microbiome health with mental illnesses, including depression, bipolar, schizophrenia, addiction, and autism. When the microbiome improves, those disorders tend to improve, perhaps by decreasing inflammation. Many people use a probiotic supplement, but I prefer food sources. A serving of kefir has several hundred times the colony-forming units of a probiotic capsule.

TCPR: Are some foods particularly challenging for patients?

Dr. Ramsey: Seafood can be a struggle. Some patients just don't like it, but I've found shrimp, smoked salmon, and even canned seafood to be good entry points. Others have concerns about mercury, microplastics, and other pollutants. Small fish like anchovies and sardines are relatively free of environmental toxins and are a great source of omega-3. Meat and seafood also raises ethical concerns for some, and we need to respect those stances.

TCPR: How do you modify the diet for vegetarians and vegans?

Dr. Ramsey: To start with, we need to understand where plant-based folks are coming from, as they've often faced opposition in the healthcare system. The concerns I have for patients on plant-based diets are low intakes of B-12, zinc, iron, and long-chain omega-3 fatty acids. We can test for some of those and, of course, supplement if needed. Many cereals and other foods are supplemented with these and marketed to vegetarians and vegans. Omega-3s are more challenging. Flax seeds have short-chain omega-3s like ALA, but the brain needs long-chain ones like EPA and DHA. Some patients following plant-based diets eat bivalves like clams and mussels, which contain omega-3s. Others take supplements, but keep in mind the omega-3 supplements that work in depression have a higher ratio (≥ 60%) of EPA, and those are all derived from fish (Sublette ME, *J Clin Psychiatry* 2011;72(12):1577–1584).

TCPR: Can you do this work with patients who have eating disorders?

Dr. Ramsey: We don't have research on that, but I wouldn't encourage it. Eating disorder therapies tend to help patients not think about food choices too much, and nutritional psychiatry revolves around getting people to deeply engage and think around their food. We don't want nutritional psychiatry to be used as a proxy for disordered eating.

TCPR: How can clinicians get training in nutritional psychiatry?

Dr. Ramsey: The American Psychiatric Association hosts trainings at their annual meetings, and our team has a digital training program at drewramseymd.com.

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

Brain-Friendly Food Swaps

If You're Eating/ Drinking This	Try This Instead
Added sugar	Honey
Alcohol	Kombucha
Breads with refined flour (white bread)	100% whole-wheat bread
Energy drinks	Green, black, or matcha tea (hot or iced)
Fruit juice	Smoothies with whole fruits, veggies, and yogurt
Ice cream	Canned pears sprinkled with cinnamon and cocoa nibs; frozen grapes
Pasta	Whole-wheat pasta
Processed meats (sausage, bacon, cold cuts)	Canned wild-caught fish
Salty snacks	Low-salt nuts, olives, feta cheese, home-cooked popcorn, home-baked kale chips, veggies dipped in hummus or nut butters
Sodas	Seltzer water with natural flavors Water infused with cucumber, mint, citrus, or berries
Sweets	Berries, dark chocolate (≥ 70% cocoa)
Vegetable oils, butter, and trans fats	Extra virgin olive oil
White rice	Brown rice, wild rice, whole-wheat couscous, or quinoa

Ultra-Processed Foods

What Qualifies: Packaged meals, hot dogs, cold cuts, bacon, sausage, soda, chips, microwave popcorn, candy, frozen desserts, sugary breakfast cereals, energy bars, bottled drinks, premixed baking items, margarine, premade sauces.

What to Do: These foods are best avoided, but if used, choose items that are low in sodium, added sugars, and chemical ingredients. The Open Food Facts app can read bar codes on food packaging and give useful nutrition scores.

Research Updates IN PSYCHIATRY

ADHD

Viloxazine for ADHD

REVIEW OF: Nasser A et al, *Int J Clin Pract* 2021;75(8):e14330

STUDY TYPE: Meta-analysis of randomized controlled trials

Viloxazine (Qelbree) just got FDA approval in 2021 for the treatment of ADHD in children and adolescents, and the FDA is reviewing data in adult ADHD. Viloxazine has a long history of use as an antidepressant in Europe. Like atomoxetine (Strattera), it is a selective norepinephrine reuptake inhibitor. Stimulants are still the most effective medications for ADHD, so how does this new nonstimulant option measure up? This meta-analysis offers a clue.

The analysis included four randomized, double-blind, placebo-controlled trials. When analyzed together, they showed viloxazine was more effective than placebo at reducing ADHD symptoms in a combined 1354 children and adolescents. On an individual level, three of the four trials were positive. All four trials used improvement in the ADHD Rating Scale (ADHD-RS) after five weeks of treatment as their primary outcome. There were two levels of improvement: a 30% improvement in ADHD-RS or a more clinically significant 50% improvement in ADHD-RS.

The authors then converted these results into more clinically relevant figures: number needed to treat (NNT) and number needed to harm (NNH). The NNT represents the number of patients a clinician would need to treat to have one positive response, after removing the placebo effect. NNH is the number a clinician would need to treat to cause harm to one patient (in this case, "harm" was defined as discontinuing the trial due to any adverse effect). An NNT under 10 is considered clinically meaningful, and an NNH over 10 is considered relatively safe or acceptable.

For these studies, the NNT was 6 (95% CI: 5–9) for the less stringent 30% improvement in ADHD-RS and 7 (95% CI: 5–10) for the 50% improvement level. The NNH was 46 (95% CI: 26–167), meaning one in 46 patients discontinued the medication due to side effects for both 30% and 50% levels of improvement. The most common side effects were somnolence, decreased appetite, and headache. By contrast, other analyses have found similar NNTs for atomoxetine (5–7) and better NNTs for traditional stimulants (2–4).

Two main weaknesses stand out. The analysis was industry sponsored and was a meta-analysis of four studies that were also industry sponsored. The other limitation is generalizability—children and adolescents with solely ADHD and no other significant mental or neurological disorder participated in these studies.

TCPR'S TAKE

In children and adolescents with ADHD, viloxazine is well tolerated with an efficacy comparable to atomoxetine but less than the stimulants. The medication is not approved in adult ADHD, but the company has submitted data for adults to the FDA that are currently under review.

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

HEARING LOSS

Listening to Depression: The Importance of Addressing Hearing Loss

REVIEW OF: Marques T et al, *Eur Arch Otorhinolaryngol* 2021; Epub ahead of print

STUDY TYPE: Randomized open-label controlled trial

Age-related hearing loss is associated with depression, poorer physical and social functioning, and decreased quality of life, but can hearing aids reverse those trends? This study examined the effects of "aural rehabilitation" (hearing aids) on depressive symptoms.

The study randomly assigned 61 patients with moderate bilateral hearing loss to either receive a hearing aid or undergo no treatment. Blinding was not possible, and the control intervention consisted of regular follow-up without any placebo treatment. The primary outcome was the change in the Geriatric Depression Scale (GDS) at four weeks. A diagnosis of major depression was not required for study entry, but the participants entered the study with an average GDS score that was just at the cutoff for clinical depression. The patients with cognitive impairment were excluded from the study.

After four weeks, the average depression score decreased from 10.63 to 6.94 in the hearing aid group, while the score in the control group went from 11.69 to 10.97, a significant difference ($p = 0.003$). Using a regression model, the authors also examined the effect of various factors on depression score: age, marital status, educational level, and BPTA (a measure of hearing loss). Investigators concluded that hearing loss was independently associated with depression, and the degree of hearing loss was the main predictive factor for depressive symptoms at study entry.

The main limitation of this study is the lack of a placebo treatment in the control arm. An intervention as profound as restoration of hearing is likely to provoke a profound Hawthorne effect, a well-known phenomenon where virtually any observation or intervention can create a positive change in behavior, at least for a brief period. Other limitations include the absence of blinding, the brevity of the study, and the disparity in age between the two groups—the treatment group was younger than the control, with an average age of 77 vs 82, a significant difference ($p = 0.013$).

TCPR'S TAKE

Many of us have seen dramatic changes in our elderly patients' functionality and demeanor with restoration of hearing, and it's nice to see that confirmed here despite the study's limitations. The findings serve as a reminder that we should probably investigate hearing loss more

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aggressively and refer for intervention when indicated.

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

SCHIZOPHRENIA

Establishing a Dose-Response Relationship for Lurasidone in Acute Schizophrenia

REVIEW OF: Srisurapanont M et al, *Sci Rep* 2021:11(1):5571

STUDY TYPE: Network meta-analysis

Lurasidone is FDA approved in schizophrenia, but we lack good evidence to guide its dosage. This study compared the efficacy, safety, and acceptability of lurasidone at different doses to establish a dose-response relationship for its therapeutic and adverse effects.

The study was a network meta-analysis of 10 randomized controlled trials with a total of 3336 adult patients with acute schizophrenia. The selected trials used fixed-dose lurasidone and lasted 4–16 weeks. Studies with a crossover design or flexible dosing were excluded. The primary outcomes were overall reduction in psychotic symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) and all-cause dropout rates. These data allowed the investigators to compare 10 independent treatments at various doses of lurasidone (20, 40, 80, 120, and 160 mg/day) against a placebo or four comparator antipsychotics.

The analysis found that all doses except the 20 mg/day were effective in acute schizophrenia. The highest dose (160 mg/day) outperformed all of the lower doses on the primary outcome of improvement in the PANSS. The "effective dose 50," which estimates the dose that produces the desired effect in at least half the population, was at least 80 mg/day.

An interesting finding arose when the investigators attempted to find the maximum effective dose by graphing the results. The graphs for psychotic symptoms, negative symptoms, and depressive symptoms continued to rise without plateauing up to the maximum approved dose of 160 mg/day, suggesting that lurasidone's maximum effective dose may be higher than that. Most side effects rose in concert with the dose, particularly sedation and EPS, but all-cause dropouts were similar across the 40–160 mg/day dose range. This suggests that the tolerability problems may be outweighed by the benefits in the higher dose range.

TCPR'S TAKE

Lurasidone requires higher dosing to reach maximum efficacy in schizophrenia, up to the official maximum of 160 mg/day and possibly beyond that. High doses did not lead to higher dropout rates, but in our experience, one particular side effect is lessened with a slow titration: akathisia.

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

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In Brief: Meds in the Fast Lane

In the last five years, more psychotropics have gained approval through the FDA's expedited pathways than the slow and cautious routes we've grown used to. These "fast-track" and "breakthrough therapy" approvals allow drugs to enter the market on the basis of more efficient (ie, smaller) clinical trials. Instead of the typical 2000 participants, many are approved through trials enrolling only 200.

For clinicians, this means the efficacy—and even more so the safety—of these expedited drugs cannot be fully trusted, particularly in the first few years of their release. Compared with traditional approvals, these drugs are 1.5 times more likely to see black box warnings added after their release (Mostaghim SR et al, *BMJ* 2017;358:j3837). In essence, our practices are the testing sites for the Phase III trials often skipped over in these approvals.

Both the fast-track and breakthrough designations require some initial evidence that the drug has the potential to fill an unmet need in a serious disorder. For that first step, the fast-track pathway allows animal studies, while the breakthrough pathway requires clinical data. In the end, both pathways require companies to provide clinical data to gain approval, but a third pathway, accelerated approval, allows biological markers to substitute for more direct clinical outcomes. For example, reduction in tumor size is a marker for cancer survival rates.

Aducanumab is the first neuropsychiatric drug to earn approval through the accelerated pathway, and the biomarker it depended on was amyloid plaques. However, it's not clear that this is a meaningful marker of dementia, and that is just the beginning of the controversies surrounding this approval, which are detailed in this issue.

Psychotropics With Expedited Approvals

Medication	Indication[1]
Aducanumab (Aduhelm, 2021)	Alzheimer's disease dementia (n = 3285)
Brexanolone (Zulresso, 2019)	Postpartum depression (n = 226)
Deutetrabenazine (Austedo, 2017)	Tardive dyskinesia (n = 404)
Esketamine (Spravato, 2019)	Treatment-resistant depression (n = 1709) Depression with acute suicidality (n = 262)
Pimavanserin (Nuplazid, 2016)	Parkinson's disease psychosis (n = 199)
Valbenazine (Ingrezza, 2017)	Tardive dyskinesia (n = 234)

[1]*Number of participants in FDA-registration trial(s)*

Biomarkers are unlikely to replace clinical outcomes in psychiatry anytime soon, but breakthrough and fast-track approvals are rapidly becoming the norm. Waiting in the wings are MDMA, psilocybin, an oral version of brexanolone (zuranolone), and combination pills for unipolar (bupropion-dextromethorphan) and bipolar depression (lurasidone-cycloserine). For patients with severe, refractory disorders, this is good news, and it's for those patients that these meds should be reserved, at least until their safety is better established. Until then, we'll need to keep our eyes wide open for unforeseen outcomes.

—Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report

CME Post-Test

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1. According to Dr. Parker, which symptom best distinguishes bipolar from unipolar disorder (LO #1)?
   [ ] a. Euphoria
   [ ] b. High levels of energy
   [ ] c. Heightened emotions
   [ ] d. A decreased need for sleep

2. Which of the following statements about the efficacy of aducanumab compared to placebo for mild cognitive impairment (MCI) and mild Alzheimer's disease is true (LO #2)?
   [ ] a. Aducanumab significantly reduced rates of cognitive decline but had no effect on functional impairment
   [ ] b. Aducanumab did not separate from placebo on the cognitive decline or functional impairment outcomes
   [ ] c. Aducanumab significantly improved functional impairment but had no effect on cognitive decline
   [ ] d. Aducanumab significantly reduced rates of cognitive decline and significantly improved functional impairment

3. In a 2011 study of omega-3 fatty acid supplementation for major depressive disorder, which percent composition of EPA out of the total EPA + DHA content was associated with improvements in depression (LO #3)?
   [ ] a. ≤ 20% EPA
   [ ] b. ≥ 40% EPA
   [ ] c. ≥ 60% EPA
   [ ] d. ≤ 50% EPA

4. In a recent study of viloxazine for ADHD in children and adolescents, the number needed to harm was 46 for medication discontinuation due to side effects (LO #4).
   [ ] a. True
   [ ] b. False

5. For patients with bipolar disorder and ADHD, which of the following medications does not increase the risk of mania (LO #1)?
   [ ] a. Modafinil
   [ ] b. Adderall
   [ ] c. Clonidine
   [ ] d. Atomoxetine

6. What was the main limitation of the finding that the highest dose of aducanumab was associated with reduced cognitive decline compared with placebo, based on changes in Clinical Dementia Rating-Sum of Boxes scores (LO #2)?
   [ ] a. The study had a small sample size
   [ ] b. There was evidence of unblinding in the study
   [ ] c. The study did not use an intent-to-treat analysis
   [ ] d. This result came from a post-hoc analysis

7. A 2021 study of bipolar and unipolar disorder by Dr. Parker and colleagues showed a clear categorical separation between normal elevated mood and hypomania (LO #1).
   [ ] a. True
   [ ] b. False

8. For acute schizophrenia, which dose of lurasidone yielded the greatest improvement on the Positive and Negative Syndrome Scale in a 2021 study (LO #4)?
   [ ] a. 20 mg/day
   [ ] b. 80 mg/day
   [ ] c. 120 mg/day
   [ ] d. 160 mg/day

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PARASOMNIAS

Sleepwalking on Antipsychotics and Lithium

REVIEW OF: Gouverneur A et al, *Br J Clin Pharmacol* 2021;87:3971–3977

STUDY TYPE: Retrospective analysis

Sleepwalking and sleep-eating are common parasomnias, also known as somnambulism and sleep-related eating disorder. Both can be side effects of benzos, z-hypnotics, and—rarely—antidepressants. This review looked at parasomnias' association with antipsychotics and lithium.

The authors used a World Health Organization database of suspected adverse drug reactions, which contains reports by physicians dating back to 1978. Lacking a control group, they compared the rate of parasomnias in the database with that in the general population to see if there was any disproportional reporting for patients on atypical antipsychotics or lithium.

They presented their data in terms of the proportional reporting ratio (PRR) for each medication—where a PRR over 1 means the parasomnia might be associated with the medication. As expected, the highest PRR by far was for the benzodiazepines and z-drugs, together at 60.51. The PRRs were also elevated for the atypical antipsychotics at 3.44 (CI 3.13–3.78) and lithium at 2.03 (CI 1.22–3.37). First-generation antipsychotics did not show a significant PRR at 0.99 (0.68–1.44),

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while antidepressants clocked in at 3.01 (CI 2.76–3.28). Atypical antipsychotics with the highest PRRs were quetiapine at 12.50 (CI 11.06–14.13), lurasidone at 7.00 (CI 3.97–12.34), olanzapine at 3.23 (CI 2.50–4.17), and aripiprazole at 2.89 (CI 2.17–3.83). Of the atypical antipsychotics, nearly all had a significant PRR except for risperidone, paliperidone, and clozapine.

The main weakness here is that data of this type are meant to find associations but cannot confirm them. Also, the results do not tell us how common the problem is, as mild cases are usually not reported to these kinds of databases.

TCPR'S TAKE

Although benzodiazepines and z-hypnotics are the medications that are most likely to cause parasomnias, these sleep problems may also occur on antidepressants, lithium, and most atypical antipsychotics.

—Thomas Jordan, MD.

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