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Chris Aiken, MD
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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. Make informed decisions when combining antipsychotics and stimulants, including considerations for tapering and withdrawal.
2. Understand the role of disease-modifying drugs in psychiatric treatment, particularly in the context of mood disorders.
3. Identify appropriate preventive interventions for individuals presenting with prodromal symptoms of schizophrenia or bipolar disorder, particularly those with a family history.
4. Summarize some of the current research findings on psychiatric treatment.

The Antipsychotic-Stimulant Combo

Avneet Soin, MD. Psychiatry resident, NYU Grossman School of Medicine. Deepti Anbarasan, MD. Associate Professor, Psychiatry & Neurology, New York University, New York. Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report; *Assistant Professor, NYU Langone Department of Psychiatry; practicing psychiatrist, Winston-Salem, NC.*

Dr. Soin, Dr. Anbarasan, and Dr. Aiken have no financial relationships with companies related to this material.

Highlights From This Issue

Feature article. Stimulant-antipsychotic combos are rarely justified but increasingly prescribed. We look at what the risks are and what to do about them.

Q&A. Dr. Nassir Ghaemi divides depression into four types: neurotic, existential, vascular, and manic-depressive illness.

Article on page 5. Psychiatric prodrome means the patient has soft signs of mental illness and genetic loading for the same. Psychotherapy and omega-3 fatty acids are good first-line interventions.

Even if you're a by-the-book psychopharmacologist, you're likely to inherit patients on unusual combinations of meds. In a recent issue, we looked at how to handle patients on benzos and stimulants (see the October/November 2022 issue of *The Carlat Psychiatry Report*). We'll continue that theme here with another unusual pairing: the antipsychotic-stimulant combo.

Combining a dopamine blocker with a dopamine agonist sounds questionable on its face, but the pairing has a long history, dating back to the 1950s when the chlorpromazine-dextroamphetamine combo pill ThoraDex was marketed for

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Q&A With the Expert

A Disease-Modifying Approach to Mood Conditions

S. Nassir Ghaemi, MD, MPH

Professor of Psychiatry and Director of the Psychopharmacology Consultation Clinic at Tufts Medical Center.

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

TCPR: You've written that we should think about whether the medications we use are "disease modifying." Tell us about that.

Dr. Ghaemi: Disease-modifying drugs address the underlying pathophysiology and improve the overall course of the illness. That's in contrast to symptomatic treatments, which reduce symptoms temporarily but don't change the course of the disease because they don't address the underlying cause. This idea is common in other fields of medicine. For example, Tylenol is a symptomatic treatment for fever, but penicillin is disease modifying.

TCPR: Which psychiatric medications are disease modifying?

Dr. Ghaemi: You could argue that lithium qualifies, and possibly other mood stabilizers like valproate, carbamazepine, and lamotrigine. Lithium normalizes the expression of the "CLOCK genes" that code for circadian rhythms

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The Antipsychotic-Stimulant Combo

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"anxious neurotics" and "alcoholics." That combo quietly left the shelves after the FDA required proof of efficacy, but the pairing is on the rise, particularly among the young. Around one in five children who are prescribed a stimulant are also prescribed an antipsychotic (Kamble P et al, *Psychiatr Serv* 2015;66(4):404–410).

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The concern here is not of a dangerous drug interaction. Rather, stimulants might worsen problems that the antipsychotic is treating, especially psychosis and mania, by increasing dopamine at the D2 receptor. Antipsychotics, meanwhile, might blunt the cognitive benefits of stimulants by blocking the cortical D1 receptor.

Stimulants in psychosis

A single dose of a stimulant causes psychosis 30% of the time when given to someone in remission from a psychotic disorder and worsens psychosis 50%–70% of the time when given during an active episode, according to an analysis of 54 studies (Curran C et al, *Br J Psychiatry* 2004;185:196–204). This risk is higher with amphetamine than methylphenidate. In a cohort study of 221,000 adolescents and young adults with ADHD, amphetamines were associated with double the risk of psychosis compared to methylphenidate formulations (Moran LV et al, *N Engl J Med* 2019;380(12):1128–1138).

Given those risks, we'd need to see significant benefits with stimulants to justify their use in psychotic disorders. Unfortunately, stimulants did not mitigate cognition problems, fatigue, or weight gain in a meta-analysis of 22 trials in psychotic disorders (Solmi M et al, *CNS Spectr* 2019;24(5):479–495). Likewise, the modafinils failed on those outcomes, and these novel stimulants bring an additional risk by lowering blood levels of many antipsychotics through CYP3A4 induction (Wittkampf LC et al, *Ther Adv Psychopharmacol* 2012;2(3):115–125).

Stimulants in mania

In bipolar disorder, stimulants raise the risk of mania, even when paired with an antipsychotic. As with psychosis, the risk of mania is worse with amphetamines, which are even used as an animal model for mania. For methylphenidate, well-designed studies are lacking, and epidemiologic studies find both benefits and harms.

Two studies have attempted to shed light on the situation by comparing rates of mania before and after starting methylphenidate in large populations of patients with bipolar disorder. These before-and-after or "mirror image" designs are prone to false conclusions, and here the results were mixed. One study found higher rates after starting the drug (but only in those not taking mood stabilizers), while the other found no difference or lower rates (regardless of mood stabilizer status) (Jefsen OH et al, *J Clin Psychopharmacol* 2023;43(1):28–34).

More reassurance comes from a long-term follow-up study in 289,840 children with ADHD and their age-matched controls. Compared to those with ADHD who never took methylphenidate, those who took it long term had a 30% lower risk of developing bipolar disorder (Wang LJ et al, *J Psychiatr Res* 2016;72:6–14).

Some have even speculated that methylphenidate might improve mania by stabilizing wakefulness and attention. That idea did not pan out in a randomized controlled trial of actively manic patients. The brief, three-day trial found no benefit but—reassuringly—also found no worsening of mania in the patients who took methylphenidate (Hegerl U et al, *Eur Neuropsychopharmacol* 2018;28(1):185–194).

Stimulants in complex patients

Stimulants are often used as a last resort in patients with complex comorbidities, many of whom are also taking an antipsychotic. Here we lack good data but see a similar pattern favoring methylphenidate over amphetamines. For example, methylphenidate improved ADHD symptoms and decision-making in a controlled trial of borderline personality disorder with ADHD, while amphetamine has a record of causing aggression and paranoia in the borderline population (Gvirts HZ et al, *Int Clin Psychopharmacol* 2018;33(4):233–237).

In a series of large observational studies from Denmark, methylphenidate but not amphetamine use was associated with a decrease in suicidality and self-harm in mood and personality disorders. These studies were limited by the "mirror image" design discussed above, which lacks randomization and cannot control for all variables (Rohde C et al, *Aust N Z J Psychiatry* 2021;55(4):422–424).

The psychiatric risks of both methylphenidate and amphetamine are magnified in the higher doses, as a study in a non-psychiatric population of 112 patients

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with narcolepsy demonstrates. Compared to patients on normal doses of stimulants, high doses were associated with a three-fold to 12-fold increase in psychosis, addiction, suicide attempts, and psychiatric hospitalizations (Auger RR et al, *Sleep* 2005;28(6):667–672).

Antipsychotics do have a role in stimulant use disorders, where they reliably reduce psychotic symptoms brought on by excessive use. They also reduce the rewarding effects of stimulants, rendering subjects in laboratory settings unable to tell if they were given a stimulant or a placebo.

Antipsychotics in ADHD

Turning to ADHD, it is the stimulant that is therapeutic and the antipsychotic that is controversial. This combination has the most support in children with ADHD who continue to have problems with aggression after successful stimulant treatment. Risperidone (0.5–3.5 mg/day) reduced aggression in two large randomized trials of that population, although valproate brought similar improvements with fewer side effects (Blader JC et al, *J Am Acad Child Adolesc Psychiatry* 2021;60(2):236–251).

Those studies did not look at whether the additional antipsychotic worsened ADHD symptoms, but three controlled studies suggest it can. In both healthy adults and children with ADHD, risperidone and haloperidol blocked the beneficial effects of stimulants on objective tests of working memory and attention (Markowitz JS et al, *Clin Pharmacokinet* 2001;40(10):753–772).

Stimulants exert their cognitive benefits through the D1 receptor, raising hopes that antipsychotics with low D1 blockade might be able to augment stimulants in ADHD (eg, aripiprazole, brexpiprazole, and cariprazine). This idea yielded mixed results in a few small trials, and it was recently tested in a large controlled trial of brexpiprazole as augmentation to stimulants in ADHD. The antipsychotic neither worsened nor improved ADHD symptoms in this manufacturer-supported trial (Reimherr FW et al, *J Clin Psychopharmacol* 2022;42(5):445–453).

Practical tips

We've found little reason to start an antipsychotic-stimulant combination, but what should we do when a patient presents on it? The decision to taper depends on the risk. Stimulants are riskiest in psychotic disorders, somewhat less risky in bipolar I, and safer when there is a valid diagnosis of ADHD. Antipsychotics are not particularly risky in ADHD, but they may worsen cognition and their side effect profile rarely outweighs their benefits in this disorder.

Unless the combination is posing a dire threat, it's best to proceed gingerly and avoid the impulse to make sudden wholesale changes. Both medications are associated with withdrawal syndromes, and little is known about long-term accommodation to the pair. Check with past providers for a possible rationale and taper slowly, if necessary, over at least two weeks and often longer. Make sure you have a good alliance with your patient before disrupting any attachment they've developed with the medicine.

CARLAT VERDICT

Off-label use of stimulants carries psychiatric risks, particularly in psychosis and mania. Those risks are greater with amphetamine than methylphenidate varieties, and greater at higher doses. Some antipsychotics may dampen the cognitive benefits of stimulants.

Expert Interview

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and are strongly linked to manic depression (Mishra HK et al, *Mol Psychiatry* 2021;26(7):3383–3394). It also reverses the hyperexcitability seen in young nerve cells derived from patients with bipolar illness (Mertens J et al, *Nature* 2015;527(7576):95–99).

TCPR: You left antipsychotics off the list of "mood stabilizers."

Dr. Ghaemi: Right. Antipsychotics (I prefer the term "dopamine blockers") are not mood stabilizers because they have not been shown to prevent mood episodes. Now, there are trials where they look preventative, but those were designed in a way that favors the antipsychotic. They withdrew the medications too soon and used "enriched samples" of patients who already responded to them, which gives false-positive results.

TCPR: What about quetiapine? Putting aside the problem with study design, most antipsychotics only prevented mania—not depression—but quetiapine prevented both poles in its long-term studies.

Dr. Ghaemi: That is true, but I don't believe those results because the company won't provide the actual data for researchers like me to analyze independently.

TCPR: How would you analyze it differently?

Dr. Ghaemi: I would be interested in the initial polarity (eg, mania vs depression), the polarity of relapse, and how long it took for the relapse to occur after stopping the drug. That's how we can tell if a truly new episode has been prevented, as opposed to just withdrawal relapse into the same acute episode that the patient had a few weeks or months earlier.

TCPR: What is different about lithium's preventative effects?

Dr. Ghaemi: For one thing, lithium is the only medication that's been proven to prevent suicide—completed and attempted—in randomized trials, and it prevents suicide in both unipolar and bipolar disorders. Clozapine is a close second. It prevented suicide attempts, but not completed suicides, in a randomized trial of schizophrenia. Lithium also prevents hospitalizations, even in unipolar depression. There was a large Finnish study that followed 123,712 unipolar patients for about eight years after hospitalization for depression. Lithium was the only med associated with a lower risk of rehospitalization (Tiihonen J et al, *Lancet Psychiatry* 2017;4(7):547–553).

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TCPR: Not antidepressants?

Dr. Ghaemi: No. Antidepressants and antipsychotics were associated with higher rehospitalization rates. Even though this was a non-bipolar group, lithium's preventative effects were greater when used on its own than when it was combined with an antidepressant (70% vs 50% rehospitalization rate). This study wasn't randomized—each patient served as their own control—but we do know from 39 controlled trials that lithium prevents depression in unipolar disorders, and it has one of the largest preventative effects in bipolar disorders (Undurraga J et al, *J Psychopharmacol* 2019;33(2):167–176). But I don't think of mood disorders in terms of bipolar and unipolar.

TCPR: What? You've developed diagnostic tools to separate bipolar from unipolar.

Dr. Ghaemi: That was when I thought the DSM was valid. In 1980, DSM-III separated mood disorders into bipolar and unipolar, using "major depressive disorder" (MDD) for "unipolar." For nearly a century before that change, psychiatrists lumped severe, recurrent mood disorders into a single category of "manic-depressive illness" regardless of whether the episodes were manic or depressive.

TCPR: Tell us more about this idea of a single manic-depressive illness.

Dr. Ghaemi: In my view, which is the same as Kraepelin's, mania and depression are part of one illness, and cycling of mood episodes is the core feature of this illness. Those episodes may be manic, depressive, or mixed (and mixed is actually the most common), and they may last three months, six months, or a year. They are severe. But the key feature is the cycling: They come and go every couple of years. Manic-depressive illness is a biological disease with genetic underpinnings, and it is best treated with lithium and mood stabilizers—especially for the long term, for prevention, but also in the short term in many people.

"In my view, which is the same as Kraepelin's, mania and depression are part of one illness, and cycling of mood episodes is the core feature of this illness."

S. Nassir Ghaemi, MD, MPH

TCPR: Why did DSM-III split this into bipolar and unipolar?

Dr. Ghaemi: The idea was that the two poles differed in their genetics and course of illness, but that has not held up so well. In genome-wide association studies, the genetics of bipolar and so-called MDD do not separate out. In terms of course of illness, that idea was based on data showing that bipolar tends to start at ages 15–20 while unipolar MDD begins around age 30. But that has also changed—at minimum, a lot of children have depression without manic episodes and receive a diagnosis of MDD. If the distinction is valid, then we should stop diagnosing MDD in all or most children. Also, many of those children with "depression" have family histories of bipolar illness, further blurring the bipolar vs unipolar distinction. The DSM also had pragmatic considerations, because it was convenient to say "We'll create a category for tricyclics (MDD) and a second category for lithium (bipolar)." But many MDD patients respond to lithium.

TCPR: What did we lose in the transition from manic depression to bipolar-unipolar?

Dr. Ghaemi: The bipolar side shrank, while the unipolar "MDD" side widened. The bipolar criteria in DSM are very strict, which means that a lot of patients with manic symptoms that don't meet the full DSM criteria for bipolar disorder will receive antidepressants. About one in four patients with MDD have manic symptoms ("mixed features") during their depression (Vázquez GH et al, *J Affect Disord* 2018;225:756–760).

TCPR: How would you classify depressions that don't fit into your concept of "manic-depressive illness," those that don't cycle in and out of recurrent mood episodes?

Dr. Ghaemi: Outside of manic depression, I see three types: 1) neurotic depression, 2) vascular depression, and 3) existential depression. Melancholic and psychotic depression are also valid categories, but I would include them under manic-depressive illness. By "neurotic depression" I'm referring to patients with the neurotic temperament, not the Freudian sense of neurosis. Neuroticism is one of the best-validated temperaments. These patients tend to be anxious all the time, and they react more to stress than the average person. When stress is high, their symptoms might meet criteria for mild MDD for a few weeks or a few months at the longest. These patients are common in practice, and with today's DSM they are usually diagnosed with MDD, sometimes with generalized anxiety disorder as well, and treated with SSRIs.

TCPR: How would you treat neurotic depression?

Dr. Ghaemi: That's difficult. This is actually why there's a vigorous debate about whether modern antidepressants even work. They do work, but mainly in severe depression. In mild depression, there is little separation from placebo, and most of these patients with neurotic depression have mild depression. This is something we didn't realize until 20 years ago when the unpublished data were released, and it is why the UK's NICE guidelines do not recommend antidepressants in mild depression (Fournier JC et al, *JAMA* 2010;303(1):47–53). So that leads me to suggest psychotherapy, or at least a therapeutic, supportive relationship for these patients.

TCPR: Tell us about vascular depression.

Dr. Ghaemi: Vascular depression typically begins in midlife in patients with cardiovascular risks, like long-standing diabetes or hypertension. It is associated with white matter abnormalities on the MRI, so there is an actual biological marker that is diagnostic and useful. You have to read the full MRI report because the summary might read "normal for age" but the narrative will mention periventricular or deep white matter hyperintensities.

TCPR: If they haven't had a brain MRI, what symptoms distinguish vascular depression?

Dr. Ghaemi: These patients may have more cognitive problems, like trouble with task completion,

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How to Identify and Treat Prodromal Symptoms of Bipolar Disorder and Schizophrenia

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Dr. Sanchez-Cruz and Dr. Aiken have no financial relationships with companies related to this material.

A 19-year-old college sophomore is brought to the clinic by her mother, who is concerned about her anxiety. Her grades have dropped, and she is "suspicious" of her roommates and has a strong feeling that "reality is not what it seems."

When a patient presents with soft signs of psychosis or bipolar disorder, how can we tell if they will go on to develop the full syndrome? Screening instruments are time consuming, require advanced training, and largely have not been validated to detect early "prodromal" symptoms. In this article, we will discuss how to identify and treat prodromal symptoms to reduce the likelihood of progression to the full disorder.

The schizophrenia prodrome

About 75% of patients with schizophrenia show early prodromal symptoms, including changes in sleep, avolition, and erratic behavior. Cannabis use is a strong predictor of progression to schizophrenia. Other risk factors include family history of psychosis, cognitive deficits, history of suicidality, adverse childhood experiences, and lower socioeconomic status (Conroy S et al, *Curr Treat Options Psychiatry* 2018;5(1):113–128; Althwanay A et al, *Cureus* 2020;12(6):e86392020).

The bipolar prodrome

Prodromal symptoms can also precede the full onset of bipolar disorder. These symptoms run the gamut of the DSM, including symptoms of ADHD, anxiety, conduct, and substance use disorder, as well as subthreshold symptoms of mania and depression. For those who convert to the full disorder, the prodromal phase lasts about two years on average. A family history of bipolar disorder is the most potent predictor of conversion to bipolar disorder, particularly in the parents or grandparents (Post RM et al, *J Affect Disord* 2020;272:508–520). Most studies define the bipolar prodrome as youth with active psychiatric symptoms and a first-degree relative with the disorder.

In one study that followed the offspring of parents with bipolar disorder for five years, it was the severity of the symptoms rather than their particular nature that predicted conversion (Diler RS et al, *Bipolar Disord* 2017;19(5):344–352). Worsening of psychiatric symptoms on an antidepressant is also a strong predictor (Conroy et al, 2018). Childhood trauma is also predictive, and patients with a history of childhood trauma also have an early onset of bipolar disorder (Post et al, 2020; Conroy et al, 2018).

Prevention

Medications, psychotherapy, and natural treatments have all been tried to prevent conversion to major psychiatric disorders, with some surprising results. Antipsychotics did not prevent conversion to schizophrenia in three trials that tested olanzapine, risperidone, and ziprasidone in patients with prodromal psychotic symptoms. Since young people are more susceptible to the metabolic side effects of these medications, most clinical guidelines do not recommend antipsychotics for prodromal psychotic symptoms (Mei C et al, *Clin Psychol Rev* 2021;86:102005).

For prodromal bipolar disorder, pharmacotherapy is poorly studied, and the evidence is not strong enough to recommend it. However, there is evidence to suggest caution with antidepressants. A small trial of paroxetine in children with depression whose parents had bipolar disorder was halted early because over half of participants developed mania on the antidepressant, regardless of whether it was used as monotherapy or in combination with valproate (Findling RL et al, *J Child Adolesc Psychopharmcol* 2008;18:615–621). Schneck and colleagues developed and tested an algorithm for children and teens who have a parent with bipolar disorder. They recommend avoiding antidepressants in patients with subthreshold mixed or manic symptoms and those with a history of mood worsening on antidepressants (Schneck CD et al, *J Child Adolesc Psychopharmacol* 2017;27(9):796–805).

Omega-3s

There is some evidence that omega-3 fatty acids prevent conversion to schizophrenia. One study randomized 81 adolescents with prodromal psychotic symptoms to a three-month course of placebo or omega-3s (700 mg EPA + 480 mg DHA daily) (Amminger GP et al, *Nat Commun* 2015;6:7934). At seven-year follow-up, those who took the brief course of omega-3s were four times less likely to develop schizophrenia (10% vs 40%).

Omega-3s also have evidence in pediatric bipolar depression, and a small randomized trial found efficacy in youth with prodromal symptoms of bipolarity (1400 mg EPA + 200 mg DHA daily). In that study, omega-3s reduced depressive but not manic symptoms after three months, as well as two to five years later in an open-label extension (Fristad MA et al, *J Affect Disord* 2021;281:24–32). However, not all studies of omega-3s for prevention of schizophrenia and bipolar have been positive.

Putting it into practice

Psychotherapy, supported by numerous trials, is more effective than medication in preventing full disorder conversion. For our 19-year-old patient with prodromal psychosis and a family history of schizophrenia, omega-3 fatty acids, family therapy, and skill-focused psychotherapy with cannabis cessation are recommended (Saraf G et al, *Lancet Psychiatry* 2021;8(1):64–75; Zheng Y et al, *Schizophr Bull* 2022;48(1):8–19).

CARLAT VERDICT

Patients with a close family history of psychotic or bipolar disorder and prodromal symptoms are at high risk of conversion to the full disorder. Psychotherapy and omega-3 fatty acids are first-line interventions and have better evidence than medication.

Research Updates IN PSYCHIATRY

DEPRESSION

Mitochondrial Modulators and Bipolar Depression

Simon M. Dosovitz, MD. Dr. Dosovitz has no financial relationships with companies related to this material.

REVIEW OF: Liang L et al, *Transl Psychiatry* 2022;12(1):4

STUDY TYPE: Systematic review and meta-analysis of randomized controlled trials

Mitochondrial dysfunction is thought to play a role in bipolar disorder, and several controlled trials have examined whether nutritional supplements that support energy production in the mitochondria can treat bipolar depression. This meta-analysis gathered that evidence together for a big-picture view.

The authors identified 13 randomized, placebo-controlled trials that investigated the antidepressive effects of specific mitochondrial modulators in bipolar depression: N-acetylcysteine (NAC; four trials); omega-3 polyunsaturated fatty acids (three trials); inositol (two trials); and one trial each of coenzyme Q10 (CoQ10), creatine monohydrate, vitamin D, and acetyl-L-carnitine/alpha-lipoic acid combination. The primary outcome was the standard mean difference (SMD, aka effect size) based on changes in the Montgomery-Åsberg Depression Rating Scale or the Hamilton Depression Rating Scale. Using Cochrane guidelines, the authors determined that there was a low risk of publication bias among the studies. The total sample size was 605.

Overall, the mitochondrial modulators significantly reduced depression severity compared to placebo, with a moderate effect size (SMD=0.48; 95% CI=[0.14, 0.83]; p=0.007). However, only NAC and CoQ10 individually demonstrated significant reductions in depression severity. Since CoQ10 was only examined in one study, the pooled effect size was mainly driven by NAC, with a wide confidence interval (CI) around NAC's effect size (SMD=0.88; 95% CI=[0.27, 1.48]; p=0.005). A wide CI means there is more uncertainty about the actual effect size of NAC. It could be as small as 0.27 or as large as 1.48, but it's important to note that even the lower end of this range still indicates a positive effect on reducing depression severity. A possible explanation for this variance is that NAC takes a long time to work. The longer-term trials (greater than four months) tend to be positive, while the short-term studies tend to be negative.

NAC is safe and well tolerated, with a recommended dosage of 2,000 mg daily.

CARLAT TAKE

We're not convinced that there is a class effect with mitochondrial agents, but NAC is worth trying when other options fail in bipolar depression and the patient prefers a nonmedication approach.

MOOD DISORDERS

Lurasidone vs Quetiapine in Bipolar Depression

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

REVIEW OF: Diao X et al, *Pharmaceuticals* 2022;15(11):1403

STUDY TYPE: Randomized, double-blind controlled trial

We have effective medications for bipolar disorder, but one in three patients continue to experience cognitive problems even after mood stabilization. In an earlier controlled trial, lurasidone (Latuda) improved cognition in patients who were in remission from bipolar episodes. This new study looked at how lurasidone and quetiapine compared in improving cognition for young people with bipolar depression.

The independently funded study enrolled 71 young participants, ages 10–17, with bipolar depression. They were randomly given either lurasidone or quetiapine for eight weeks, using a double-blind design. The primary outcome was cognition as measured with the THINC-it app, a free computerized test that assesses processing speed, working memory, and executive functioning (available at https://progress.im/en/content/download-thinc-it%C2%AE-tool). The researchers also looked at secondary outcomes like depression and metabolic side effects.

The study found that participants on lurasidone performed better on a test of working memory than those on quetiapine. They were faster (p=0.008) and more accurate (p=0.012) on the test. But the two groups didn't show any significant differences on the other tests or on the secondary outcomes like depression and metabolic side effects. Because the study didn't include a placebo group, the researchers couldn't say for sure whether the improvements were due to the medication or some other factor.

Limitations included a small sample size from a single center, a high dropout rate, and a lack of a placebo group.

CARLAT TAKE

Lurasidone might have a cognitive advantage over quetiapine, but we'll wait for larger trials before jumping to that conclusion.

Expert Interview

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trouble with decision-making, and slow processing speed, but symptoms don't distinguish vascular depression very well. Vascular depression can also overlap with manic depression, and it often does because vascular disease begins earlier and is much more common in this population. If we look at all cases of depression, about one in five have evidence of vascular depression after age 50, one in two after age 65, and nearly 100% by age 75 (Taylor WD et al, *Am J Psychiatry* 2018;175(12):1169–1175).

TCPR: How do you treat vascular depression?

Dr. Ghaemi: Vascular depression does not respond well to antidepressants (Aizenstein HJ et al, *BMC*

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CME Post-Test

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1. What is the primary concern when combining antipsychotics and stimulants (LO #1)?
   - [ ] a. Dangerous drug interactions between the medications
   - [ ] b. Potential worsening of psychosis or mania in patients with bipolar or psychotic disorders
   - [ ] c. Increased risk of suicidal ideation and self-harm
   - [ ] d. Stimulant abuse and misuse

2. Which medication has been proven to prevent suicide in both unipolar and bipolar disorder (LO #2)?
   - [ ] a. Antidepressants
   - [ ] b. Lithium
   - [ ] c. Antipsychotics
   - [ ] d. Valproate

3. Which is NOT associated with an increased risk of progression to schizophrenia in individuals presenting with prodromal symptoms (LO #3)?
   - [ ] a. A family history of psychosis
   - [ ] b. Cannabis use
   - [ ] c. Cognitive deficits
   - [ ] d. A family history of bipolar disorder

4. In a study by Liang and colleagues, which mitochondrial modulator significantly reduced depression severity in bipolar depression (LO #4)?
   - [ ] a. Omega-3 polyunsaturated fatty acids
   - [ ] b. Vitamin D
   - [ ] c. N-acetylcysteine (NAC)
   - [ ] d. Inositol

5. What do studies suggest about the use of antipsychotics in combination with stimulants for treating ADHD (LO #1)?
   - [ ] a. Antipsychotics reliably improve the cognitive effects of stimulants in ADHD
   - [ ] b. Antipsychotics may reduce aggression in children with ADHD after successful stimulant treatment, but their risks make this a treatment of last resort
   - [ ] c. Stimulants and antipsychotics have a synergistic effect in improving ADHD symptoms
   - [ ] d. Antipsychotics should be avoided altogether in ADHD patients to prevent adverse effects

Expert Interview

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Med 2016;14(1):161). The most important thing is to address the cause—make sure their metabolic and cardiovascular risks are being addressed, particularly hypertension. I would also consider low-dose lithium, like 150 mg/day, because these patients are at high risk for dementia and low-dose lithium has evidence to prevent that (see the September 2022 issue of *The Carlat Psychiatry Report:* "Low-Dose Lithium to Delay Dementia?" by James Phelps, MD). Lithium is neuroprotective, and it improved motor recovery after a stroke in a small randomized, placebo-controlled trial at a medium dose of 600 mg/day (Mohammadianinejad SE et al, *Clin Neuropharmacol* 2014;37(3):73–78). Just watch for drug interactions with lithium and antihypertensives.

TCPR: Tell us about your final category: existential depression.

Dr. Ghaemi: These are depressive states that are caused by problems that are common to human existence, such as life crises or transitions. These crises can include divorce, loss of a relationship, starting a new relationship, losing a job, getting a job, grief, death of a loved one, or one's own medical illnesses. Existential depression can happen in manic-depressive illness, and often does—because the illness itself can rob people of a meaningful role in life. But I would reserve this fourth diagnosis for people who do not have the other three depressions I've discussed: manic depression, neurotic depression, and vascular depression. One way of defining existential depression is Viktor Frankl's concept that it is a normal psychological response to abnormal experiences or environments. Another way is to see it as just part of normal life, of the "limit situations" of life, as Karl Jaspers put it. And psychotherapy is the best treatment—not medication.

TCPR: Let's get back to your concept of manic depression. What is the role of antidepressants there?

Dr. Ghaemi: Antidepressants are not disease modifying, but they do give short-term symptomatic benefit for some, particularly those with more severe episodes who lack a history of manic or mixed symptoms. Even then, it is a pretty limited benefit. The problem is that they can worsen the course of manic-depressive illness, particularly in those with a history of rapid cycling, and cycling is the core feature of this illness (Ghaemi SN, *J Clin Psychiatry* 2021;82(1):19m13136).

TCPR: How do you tell the difference between rapid cycling and someone with a neurotic temperament who keeps having major stress?

Dr. Ghaemi: Well, it does take some clinical nuance, and indeed patients with manic-depressive illness also have temperamental problems that lead them into these reactive depressions. About half of patients with manic depression

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are basically normal in between their mood episodes. The other half have mood temperaments like cyclothymia (chronic mild symptoms of mania and depression), dysthymia (chronic mild depressive symptoms), and hyperthymia (chronic mild hypomanic symptoms) (Vöhringer PA et al, *J Affect Disord* 2012;136(3):577–580). What separates these patients from neurotic depression is their family histories and the severity of their mood episodes. While some of their episodes are brief and mild, they usually have some more severe episodes lasting months. Whether or not they are triggered by life stressors is irrelevant to the diagnosis. They will usually have evidence of manic-depressive illness in close relatives, either of bipolar disorder or severe unipolar depression.

TCPR: Just to poke at this concept a little more, neuroticism is also heritable, so what if the patient says "My mom was often anxious and depressed"? How do we know if the mom had neuroticism or manic-depressive illness?

Dr. Ghaemi: Neuroticism is not as heritable as manic-depressive illness but is still about 50% genetic. In manic-depressive illness, that mother would be more likely to have had severe episodes that put her out of work or required hospitalization, but that can be difficult to tell without interviewing the relative.

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

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