We know a lot about when to start medications but little about when to stop them. In this article, I'll highlight treatments that are best started with an endpoint in mind.

**Antidepressants**

Long-term antidepressant use is on the rise, but in some situations a brief course is ideal. Specifically, patients who have had fewer than three episodes can usually taper off their antidepressant after six months of recovery. Waiting longer does not confer additional benefits, but coming off before the six-month mark raises the risk of relapse by up to 11-fold (Baldessarini RJ et al, *J Clin Psychopharmacol* 2015;35(1):75–76). When stopping the antidepressant, a slow taper over two to four weeks prevents relapse better than abrupt.

**Cardiovascular Psychiatry: Part 1**

**Margo C. Funk, MD, MA, FACLP**

**Director of Cardiovascular Psychiatry, Vice Chair for Education, Residency Program Director, Department of Psychiatry, Brigham and Women's Hospital, Boston, MA.**

Dr. Funk has disclosed that in 2021, she received fees as a consultant for Acadia Pharmaceuticals. Dr. Aiken has reviewed this educational activity and has determined that there is no commercial bias as a result of this financial relationship.

**TCPR**: A lot of meds have warnings about their use in “heart disease.” Does that term include cardiac risk factors like hypertension or high cholesterol?

**Dr. Funk**: These warnings specifically refer to known heart abnormalities (eg, arrhythmias or other conduction problems), structural problems like valve disease, congenital defects, damage from myocardial infarction (MI), and congestive heart failure. Now, people with cardiovascular risk factors may have undiagnosed underlying heart disease. We are also worried about people who have vascular disease, which could include coronary artery disease (CAD) in people who’ve never had a heart attack or peripheral vascular disease in people who’ve never had a stroke. So, a better term than “heart disease” is “cardiovascular disease,” since we are concerned about the entire vascular system.

**Cardiovascular Psychiatry: Part 2**

**Margo C. Funk, MD, MA, FACLP**

**Music for Sleep**

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

**Learning Objectives**

After reading these articles, you should be able to:

1. Navigate start and stop points for hypnotics and augmentation agents in mood disorders.
2. Understand the cardiovascular effects of psychiatric medications.
3. Develop an empirically supported music protocol for patients who prefer a nonpharmacologic approach to insomnia.
4. Summarize some of the current research findings on psychiatric treatment.
THE CARLAT REPORT: PSYCHIATRY

Expert Interview — Cardiovascular Psychiatry: Part 1

Continued from page 1

TCPR: What do we worry about with psychiatric medications and cardiovascular disease (CAD)?

Dr. Funk: Let’s start with CAD, which means the patient has had angina on a stress test, ischemia on the electrocardiogram (ECG), or atherosclerosis detected on imaging studies. I avoid stimulants and tricyclics in CAD because they can raise the risk of stroke and MI, and in fact tricyclics are absolutely contraindicated in the six months following an MI. Medications that block cardiac sodium channels, including tricyclics and many anticonvulsants, may delay cardiac conduction or unmask conduction abnormalities, resulting in life-threatening arrhythmias. With clozapine, we worry about the risk of myocarditis and cardiomyopathy. Another problem is prolongation of the QT interval. Many medications prolong the QT, and when combined with other risk factors, that can result in torsades de pointes (TdP), a serious arrhythmia.

TCPR: Pharmacists often warn us when our patient is on multiple medications that prolong the QT interval. When do you put the brakes on?

Dr. Funk: One where I would put the brakes on is methadone. The risk of TdP is high with this one, so I would avoid it with other medications that prolong the QT. Methadone’s QT effects are dose-dependent, so the risk is even higher with CYP2D6 poor metabolizers at CYP enzymes. Hepatic or renal impairment could worsen the QT effects of methadone. It's crucial to consider the overall health status. Bradycardia is a big risk for TdP, as well as electrolyte imbalances, specifically hypokalemia, hypermagnesemia, and hypocalemia. This includes people with eating disorders and those who require hemodialysis. People in the ICU are at higher risk, as well as those with poor kidney or liver functioning, in part because these problems can raise levels of higher-risk medications.

TCPR: What are other risk factors?

Dr. Funk: There are modifiable and nonmodifiable risk factors (Editor’s note: See the table “Risk Factors for Torsades de Pointes”). The nonmodifiable ones include older age, female sex, and personal history of arrhythmia or structural or functional cardiac disease. Look for a family history of sudden cardiac death (SCD), as this can point to familial long-QT syndrome or genetic cardiomyopathies that predispose to SCD. Modifiable risk factors include other medications and the patient’s overall health status. Bradycardia is a big risk for TdP, as well as electrolyte imbalance, specifically hypokalemia, hypermagnesemia, and hypocalemia. This includes people with eating disorders and those who require hemodialysis. People in the ICU are at higher risk, as well as those with poor kidney or liver functioning, in part because these problems can raise levels of higher-risk medications.

TCPR: Are there meds that raise the QT interval without raising the risk of TdP?

Dr. Funk: The link between prolonged QT and TdP is not a straight line, but it’s difficult to be precise here because TdP is a difficult outcome to study. Most of the data used to categorize the risk of TdP in registries like CredibleMeds are based on weak levels of evidence like case reports and retrospective cohort studies.

TCPR: Which antidepressants are safest in cardiovascular disease?

Dr. Funk: Sertraline. We have a lot of safety data to back this one up (Parissis J et al, J Pain 2014;15(4):321–337). Other high-risk medications include the antiarrhythmics sotalol and dofetilide. Aside from these medications, which necessitate extreme caution, it is essential to perform a risk-benefit assessment for each patient, weighing the risk of TdP versus the psychiatric risk from not giving a particular psychotrophic. The QT is only one component of that assessment.

Table: Risk Factors for Torsades de Pointes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Nonmodifiable</th>
<th>Modifiable</th>
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<tbody>
<tr>
<td>Female sex</td>
<td>Multiple QT-prolonging medications</td>
<td></td>
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<tr>
<td>Older age</td>
<td>Drug toxicity</td>
<td></td>
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<tr>
<td>Structural or functional heart disease</td>
<td>Drug-drug interactions</td>
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<tr>
<td>Congenital long-QT syndrome</td>
<td>Severe acute illness</td>
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<tr>
<td>Personal history of drug-induced QT prolongation</td>
<td>Bradycardia</td>
<td></td>
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<tr>
<td>Family history of sudden (or aborted) cardiac death</td>
<td>Hypokalemia, hyponagmesemia, hypocalemia</td>
<td></td>
</tr>
<tr>
<td>Poor metabolizer at CYP enzymes</td>
<td>Hepatic or renal impairment</td>
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Continued on page 3
al, *Expert Opin Pharmacother* 2007;8(10):1529–1537). I’m also comfortable with bupropion. It causes a mild tachycardia, which may actually protect against TdP. Sometimes, though, bupropion can raise blood pressure. SNRIs and mirtazapine are generally safe. Venlafaxine can raise blood pressure and has some mixed data regarding QT prolongation, but in general the risk is negligible. Trazodone prolongs the QT in overdose, but not in normal doses. The other SSRIIs are safe as well, except citalopram, which has a more complicated safety profile.

**TCPR: Citalopram has a specific warning about TdP, correct?**

**Dr. Funk:** Yes. In 2011, the FDA warned that citalopram “should not be used” at doses above 40 mg/day, and the cutoff is even lower—20 mg/day—if the patient 1) is over 60, 2) is a poor metabolizer at CYP2C19, or 3) has hepatic impairment. Interestingly, this guidance was based on the FDA’s assertion that doses of 60 mg/day were no more efficacious than 40 mg/day. In 2012, the FDA downgraded the language in both statements from “should not be used” to “is not recommended.” They also recommended discontinuing citalopram in anyone with a QTc greater than 500 ms. These recommendations are controversial, though. Citalopram does prolong the QT interval more than other SSRIIs, but we lack clinical evidence that it raises the risk of TdP. In fact, two very large studies compared high doses of citalopram and escitalopram to equivalent doses of other SSRIIs and found that neither was associated with an increased risk of ventricular arrhythmia, sudden cardiac death, or mortality (Ray WA et al, *J Clin Psychiatry* 2017;78(2):190–195; Zivin K et al, *Am J Psychiatry* 2013;170(6):642–650).

**TCPR: What is your bottom-line recommendation? Should we feel safe prescribing citalopram in patients without cardiovascular illness?**

**Dr. Funk:** Yes, and I would also caution against reflexively changing citalopram. There are many data showing adverse psychiatric outcomes when citalopram was reflexively lowered in response to these warnings (Rector TS et al, *Am J Psychiatry* 2016;173(9):896–902).

**TCPR: What about tricyclics and MAOIs?**

**Dr. Funk:** With tricyclics, the concern is conduction delays. They should be avoided in patients with bundle-branch block or a widened QRS. I would also avoid MAOIs in cardiac disease. These patients tend to be on a lot of medications, and many are on special diets, so the risk of food and drug interactions goes up, and the complications of hypertensive crisis are much more serious.

**TCPR: Stimulants have cardiac warnings. Is that related to TdP?**

**Dr. Funk:** No, it isn’t. Stimulants raise blood pressure and heart rate, can cause coronary vasospasm, and are linked to very rare cases of sudden cardiac death. An ECG is not required before starting a stimulant, because the pretest probability is so low, but if you do have access to an ECG, you should check it. What you’d be looking for is ventricular conduction delay, arrhythmias, heart block, and recent MI. One problem with stimulants is that we don’t have many data in older adults. What I would recommend in older adults is to monitor heart rate and blood pressure at least every six months, and get an ECG once a year, depending on the patient’s other cardiac risk factors.

**TCPR: Are there mood stabilizers you worry about in cardiovascular disease?**

**Dr. Funk:** Yes. Many of the anticonvulsants block sodium channels like tricyclics do, so we worry about ventricular conduction delay and heart block. Carbamazepine, oxcarbazepine, topiramate, and lamotrigine are all on that list, and lamotrigine has a new black box warning about this. I would avoid these medications in people with ventricular conduction delays, meaning a QRS complex that is 110 ms or greater (normal is 80–100 ms). Depakote, gabapentin, and pregabalin are fairly safe here.

**TCPR: When would you worry about lithium in cardiovascular disease?**

**Dr. Funk:** Lithium is associated with sinus node dysfunction, atrioventricular block, Brugada syndrome, and QT prolongation at high doses. In general, if a patient is in treatment for one of these conditions and follows with a cardiologist, I would consult with the cardiologist before starting lithium. It is not necessary to order an ECG before starting lithium in every patient, but it is appropriate for patients who have known QT prolongation, are taking QT-prolonging medications, or have other cardiac risk factors.

**TCPR: We often see QT prolongation with antipsychotics. Which ones have the highest and lowest risk of TdP?**

**Dr. Funk:** In the lower risk category are aripiprazole and lurasidone. The highest risk is with thioridazine, chlorpromazine, and possibly ziprasidone. Olanzapine, quetiapine, risperidone, and haloperidol are middle of the road. One that is interesting is IV haloperidol, which has a reputation for causing more TdP than the oral form. This misconception was largely debunked in a recent paper, which found that much of the increased risk was due to the fact that patients in the ICU are not only more likely to get the IV form, but also typically have numerous risk factors for TdP by nature of being severely ill (Beach SR et al, *Gen Hosp Psychiatry* 2020;67:42–50). Basically, I would avoid the high-risk antipsychotics in patients with multiple additional risk factors for TdP and be careful about the middle-of-the-road ones.

*Editor’s note: See the second part of our interview with Dr. Funk on page 5.*
discontinuation. An even longer taper, such as over three to 18 months, is sometimes necessary when the patient has been on the medication for many years or has problematic withdrawal symptoms.

For recurrent depression, antidepressants have preventative effects, but psychotherapy may have even more. In a recent network meta-analysis, psychotherapy increased the odds of sustained remission from depression 1.5-fold over pharmacotherapy (Furukawa TA et al, World Psychiatry 2021;20(3):387–396).

The preventative promise of psychotherapy is the inspiration behind the sequential treatment approach, which starts with an antidepressant for acute symptom relief. If the patient responds, they are kept on the antidepressant for another three months, at which point the medication is tapered while an active form of psychotherapy is added (eg, cognitive behavioral therapy [CBT], mindfulness-based CBT, or well-being therapy). This sequential treatment approach prevented depression as effectively as antidepressant continuation in 11 randomized controlled trials (Guidi J and Fava GA, JAMA Psychiatry 2021;78(3):261–269).

Exercise is another effective pathway for prevention. In a randomized trial from Duke, aerobic exercise and sertraline had similar antidepressant effects after four months, but only exercise was successful at preventing depression 10 months later, with relapse rates of 8% for exercise vs 38% for sertraline (Baboyak M et al, Psychosom Med 2000;62(5):633–638).

If therapy and exercise are not feasible, the best course is usually to continue the antidepressant in patients who’ve had at least three past episodes. Continuation is not bulletproof, but it reduces the relapse risk from 40% to 20% over a follow-up period of six to 12 months, according to a meta-analysis of 40 trials (Kato M et al, Mol Psychiatry 2021;26(1):118–133).

Antidepressant augmentation
Antidepressant adjuncts like lithium and the antipsychotics carry long-term risks that make time-limited treatment desirable. Research in this area is scant, but studies on the topic suggest that patients need at least three months of recovery before stopping these agents. Most experts wait longer—at least six months—mirroring the time course for standard antidepressant continuation.

In my own practice, about 40% of patients are able to taper from adjunctive therapies after six months but another 60% are not. Sometimes there is good reason to continue the augmentation besides episode prevention. Lithium, for example, has robust anti-suicide effects, and the risk of suicide rises in the first month after lithium is stopped (Song J et al, Am J Psychiatry 2017;174(8):795–802). A slow taper—over at least two weeks and preferably several months—is necessary when discontinuing lithium to prevent rebound mood episodes (Baldessarini RJ et al, Bipolar Disord 2022;24(7):720–725).

Antimanic augmentation
Antipsychotics are also added to mood stabilizers to treat breakthrough mania, and here we have greater clarity on how long to continue the adjunct. An independently funded study randomized 159 patients who had recovered from mania with risperidone or olanzapine augmentation to either remain on the antipsychotic or switch to a placebo after a brief period of recovery (two to three weeks) or a longer period (six months). Early discontinuation led to higher relapse rates, but continuation beyond six months offered no protective benefits over placebo (Yatham LN et al, Mol Psychiatry 2016;21(8):1050–1056).

Hypnotics in depression
Patients with depression often remain on a hypnotic long term, but a recent study suggests they may be able to stop the hypnotic after their depression has resolved. The study began by randomizing patients with major depression and insomnia to either zolpidem CR (Ambien CR) or a placebo for sleep while simultaneously starting them on an SSRI. The patients were advised from the start that the sleep medication would only be temporary and would be abruptly stopped at the end of the trial.

As expected, patients slept better on zolpidem, but the surprise came at the end of the two-month trial when the hypnotic (or placebo) was abruptly stopped. Sleep did not worsen, and in fact it continued to improve off the zolpidem (McCall WV et al, Am J Psychiatry 2019;176(11):957–965).

This benefit may be unique to depression, as it was not seen in trials of primary insomnia or generalized anxiety disorder with insomnia. In those conditions, patients gradually lost some—but not all—of the gains in sleep after the z-hypnotic was discontinued. However, they did not “rebound” with acute worsening of insomnia, offering some reassurance that z-hypnotics do not have significant withdrawal effects (Ancoli-Israel S et al, Sleep 2010;33(2):225–234).

Putting it into practice
There are many other scenarios where time-limited treatment is ideal. The prevalence of anxiety disorders goes down after age 60, allowing a potential taper of anxiolytic medications. Likewise, adolescents may grow out of ADHD as they enter adulthood, although new studies suggest the symptoms are more likely to wax and wane than fully resolve in adulthood (Sibley MH et al, Am J Psychiatry 2022;179(2):142–151).

Medication side effects may improve over time, allowing cessation of antides with propranolol or benzotropine. On the other hand, some side effects get worse in old age, shifting the risk-benefit balance in favor of deprescribing the causative med. Examples include tardive dyskinesia, anticholinergic effects, fall risks, and—with serotonergic antidepressants—osteopenia.

In practice, time-limited treatment encounters numerous obstacles. Patients may have a psychological attachment to the medication. They may experience withdrawal effects that they confuse with relapse, or the drug may have rewarding properties that they confuse with therapeutic effects (particularly with benzodiazepines, z-hypnotics, and stimulants). To increase the chance of success, try the following:
**Cardiovascular Psychiatry: Part 2**

**Margo C. Funk, MD, MA, FACLP**

Director of Cardiovascular Psychiatry, Vice Chair for Education, Residency Program Director, Department of Psychiatry, Brigham and Women’s Hospital, Boston, MA.

Dr. Funk has disclosed that in 2021, she received fees as a consultant for Acadia Pharmaceuticals. Dr. Aiken has reviewed this educational activity and has determined that there is no commercial bias as a result of this financial relationship.

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**TCPR:** I understand depression worsens cardiovascular disease, but cardiovascular disease can also cause depression. Tell us about this “vascular depression.”

**Dr. Funk:** The idea here is that people with microvascular disease have lots of small ischemic injuries to the brain that build up and cause depression. Vascular depression is actually quite common in older adults and those with cardiovascular risk factors like hypertension, dyslipidemia, diabetes, as well as inflammation—anything that disrupts the vascular system. You can also see vascular depression in people with preexisting mood disorders because, like you said, the causation runs both ways. Cardiovascular disease is more common in mood disorders and starts earlier—six years earlier in major depression and 17 years earlier in bipolar I (Goldstein BI et al, *J Clin Psychiatry* 2015;76(2):163–169).

**TCPR:** How do you know if a patient has vascular depression?

**Dr. Funk:** Consider it if they are over age 50 and have cardiovascular risk factors like hypertension, diabetes, dyslipidemia, arterial disease, or stroke—any place where you’re seeing an insult to the vasculature. About half of older adults with depression have evidence of a vascular contribution on MRI, and the rate goes up with age (Park JH et al, *J Affect Disord* 2015;180:200–206).

**TCPR:** What would you see on an MRI?

**Dr. Funk:** An MRI is not necessary to diagnose vascular depression, but if you have one, it is worth looking at. I would look for diffuse microvascular disease or white matter abnormalities. The summary might read “normal for age,” but the full report may indicate those findings.

**TCPR:** How do you treat vascular depression?

**Dr. Funk:** It is not easy. Antidepressants do not work well in these cases, so you may have to try other approaches. The first thing is to make sure they are addressing the vascular disease not just with medication, but also with lifestyle (like physical activity) and a healthy diet (eg, Mediterranean diet, low-cholesterol diet, or the DASH diet for hypertension). After that, electroconvulsive therapy and transcranial magnetic stimulation have some evidence (Jellinger KA, *J Neural Transm (Vienna)* 2022;129(8):961–976).

**TCPR:** What do psychiatrists need to know about pacemakers and other cardiac devices?

**Dr. Funk:** First, find out what they are used for. Pacemakers are usually implanted to correct a low heart rate. Implantable cardioverter-defibrillators (ICDs) are there to terminate a potentially lethal arrhythmia that is shockable. ICDs also have pacemaking function. If someone develops torsades de pointes (TdP), the ICD will shock them out of it, but you’d still need to do something to address the underlying cause of the TdP.

**TCPR:** What is it like to live with an ICD?

**Dr. Funk:** It can be frightening. Many people with ICDs implanted for secondary prevention have already experienced a cardiac arrest. These patients are at risk for depression, anxiety, PTSD, and worsened quality of life. Their ICD can go off at any time to treat a dangerous rhythm. In some cases, it can fire multiple times, called an “ICD storm.” This is extremely painful and scary, and patients often have PTSD as a result. These storms may be from inappropriate sensing or from actual cardiac events. So, while the ICD may treat an episode of TdP, it won’t prevent it and can certainly result in psychological trauma. A useful scale to screen for ICD-associated anxiety is the Florida Shock Anxiety Scale (Kuhl EA et al, *Pacing Clin Electrophysiol* 2006;29(6):614–618).

**TCPR:** What is cardiac resynchronization therapy (CRT)?

**Dr. Funk:** You’ll see CRT used in congestive heart failure. It is an implanted electronic device that paces both sides of the heart to reduce strain. These devices can also have a defibrillation function (called a CRT-D) that operates like an ICD, with the risk of traumatic ICD storm.

**TCPR:** Thank you for your time, Dr. Funk.
Dr. Koskey has no financial relationships with companies related to this material.

The first known lullaby was recorded on a cuneiform tablet in Babylonia about 4,000 years ago, and the use of music to aid sleep has continued right up through the age of Spotify. Music therapy is cheaper, easier, and safer than standard insomnia treatments, but is it a sound recommendation to make for our patients?

A look at the data
Music therapy for insomnia is not supported by the kind of large clinical trials that would pass muster at the FDA, but it does have empirical support. The best of these studies compared music to usual care in 1,007 subjects (Jespersen KV et al, J Sleep Res 2019;28(4):e12817).

There are other problems with this research. Although most studies used blinded raters, it wasn't possible to blind the subjects (or “deafen” them, as it were) to the intervention. The studies were also small and depended on subjective reporting. When they did include objective measures of sleep like polysomnography, the effects were usually not significant. In contrast, objective measures improve with hypnotics and cognitive behavioral therapy for insomnia (CBT-I), although these changes are usually mild.

Music can, of course, have observable physiological effects on listeners. Blood pressure, respiration, and heart rate can change tempo in response to musical cues, a phenomenon called entrainment (Bernardi L et al, Circulation 2009;119(25):3171–3180). Musical crescendos are associated with vasoconstriction, and relaxing music correlates with reduced blood pressure and vasodilation in listeners. The ambient music trio Marconi Union deliberately attempted to entrain relaxation through their composition “Weightless,” which reduced blood pressure and anxiety in a small study of healthy volunteers. The piece starts at 60 beats per minute (bpm) and gradually slows over the next eight minutes to finish at 50 bpm.

A musical protocol
There is no right way to apply music for sleep. In most studies, subjects listened to relaxing music for 30–60 minutes before bed. Headphones worked as well as speakers, and music worked regardless of whether subjects were simply instructed to listen to it or were given more complicated relaxation instructions. Sometimes the music cut off after a set time and sometimes it played through the night.

Although most studies involved relaxing music, there was no secret formula to the tunes, and the intervention worked just as well when the researchers selected the tracks as when the subjects did. Familiar tunes without lyrics were preferred, as were slow tempos, regular rhythms, bass tones, and tranquil melodies. Successful trials drew from Western, Indian, and Chinese classical; new age; Gregorian chant; Celtic; and electronic music (such as binaural beats in the 5–7 Hz theta range). One piece that rose to the top in a comparative study was “Weightless,” the ambient track by Marconi Union referenced above.

Even nonrelaxing music can be beneficial, as long as it’s enjoyable. Simply enjoying music of any sort may be helpful (Dickson GT and Schubert E, Sleep Med 2019;63:142–150). A 2020 randomized controlled trial pitted an album called The Most Relaxing Classical Music against sleep music self-selected by study subjects. A total of 95 university students with self-reported difficulty sleeping were randomized to the Most Relaxing group, the bring-your-own group, or a no-music control for four weeks. The prescribed album featured slow, calm pieces such as Pachelbel’s “Canon” and Debussy’s “Clair de Lune.” The self-selected music was not necessarily slow or relaxing. In fact, over 75% of subjects chose Western and Japanese pop, anime, and video game tunes. After a month, both music groups showed similar improvements on the PSQI, while sleep did not change in the nonmusic controls (Yamasato A et al, Tokai J Exp Clin Med 2020;45(4):207–213).

In addition to acting through relaxation, entrainment, and enjoyment, music may also benefit sleepers by masking unwanted environmental sounds, the way white noise does (Dickson and Schubert, 2019). Music can provide a helpful source of distraction for patients who struggle with depressive rumination or posttraumatic anxiety at night, and it is much better than watching TV in the bedroom with its sleep-disrupting blue light.

Distraction may become discordant for some, however. One paper reported
BIPOLAR DISORDER

Do Antidepressants Have Any Role in Acute Bipolar Depression?

Marilyn J. Vaché, MD. Dr. Vaché has no financial relationships with companies related to this material.

REVIEW OF: Hu Y et al, Psychiatry Res 2022;311:114468
STUDY TYPE: Meta-analysis

Antidepressants are thought to cause mania, mixed states, and rapid cycling in bipolar disorder, but they remain the most commonly prescribed medication in this illness. The last meta-analysis on this controversial subject found a small benefit in depressive symptoms (effect size 0.17) but no change in remission or response rates with their short-term use (McGirr A et al, Lancet Psychiatry 2016;3(12):1138–1146). The current paper updates that work with 13 additional trials, adding newer studies and including some in Chinese and French.

The analysis included 19 randomized placebo-controlled trials that tested antidepressants as add-ons to mood stabilizers or antipsychotics in acute bipolar depression (not manic or mixed). The studies included 2,587 patients, only 11% (280) with bipolar II. Most studies followed them for six to 10 weeks. Investigators treated real-world patients, both inpatient and outpatient, some with substance use, psychotic symptoms, and rapid cycling. The primary outcome was response, as measured by >50% improvement in depressive rating scales or a Clinical Global Impression-Improvement score of 1–2. Secondary outcomes included remission, time to remission, adverse reactions, mood switching, and dropouts. They also compared secondary outcomes: remission rates and time to remission, adverse reactions, mood switching, and dropouts.

Response rates were available for 16 studies. In those, 59% of the subjects on antidepressants achieved response, compared with 51% on placebo (RR=1.10). Eleven studies measured remission. In those, 49% of subjects on antidepressants achieved remission, compared with 42% on placebo (RR=1.09). Neither the response nor remission rates were statistically significant. Mood switching occurred in about 5% of patients in treatment and placebo arms, and neither arm proved better at preventing adverse reactions or dropouts.

Researchers then looked at whether antidepressants performed differently when paired with a traditional mood stabilizer (lithium, valproate, or carbamazepine) vs an antipsychotic. The results for antipsychotics looked better, but close analysis showed that two of the four antipsychotic trials were industry sponsored and larger than the others, weighing the statistical outcomes in their favor.

The authors identified quality concerns in about half of the studies. Chinese researchers did not describe randomization methods and presented open-label data in eight out of 10 articles. Nonetheless, their outcomes were not significantly different from other trials.

CARLAT TAKE
Antidepressants neither help nor harm bipolar depression in the short term, at least in bipolar I disorder, which accounted for 89% of the subjects in these trials. However, longer-term studies have linked antidepressants to rapid cycling in patients with bipolar disorder.

DEPRESSION

L-Methylfolate May Offer Modest Boost to Antidepressants

Glen Spielmans, PhD. Dr. Spielmans has no financial relationships with companies related to this material.

REVIEW OF: Maruf AA et al, Pharmacopsychiatry 2022;55(3):139–147
STUDY TYPE: Meta-analysis

L-methylfolate is a metabolite of dietary folate and is approved by the FDA as a medical food for the adjunctive treatment of depression. Approval of medical foods does not require the same level of rigor as actual approval of a medication, and therefore researchers conducted a meta-analysis scrutinizing the strength of the available empirical evidence for L-methylfolate in depression.

A systematic literature search turned up only four randomized placebo-controlled trials of methylfolate as an adjunct to antidepressant treatment. Most of the trials added methylfolate after failure of an antidepressant, usually an SSRI or SNRI. Two enrolled patients with treatment-resistant depression (n=265), while the other two included patients without treatment resistance (n=284). Three trials used 15 mg/day dosing, while one used 7.5 mg. Trial duration ranged from one month to six months. Results showed a modest treatment effect on Hamilton Depression Rating Scale scores (effect size 0.38, p<0.001) and a similar effect on response rate (RR=1.26, p=0.005). The 7.5 mg dose showed no efficacy—only the 15 mg dose was effective.

The analysis had several limitations. One of the trials lacked clarity on the psychiatric medications that subjects were taking in addition to L-methylfolate, and two of the trials lacked specific data on adverse events. Two were industry sponsored, and the small number of published studies leaves open the possibility that any (unknown) unpublished studies with negative findings could greatly reduce the apparent effect of L-methylfolate.

On the other hand, the authors did not include a large randomized controlled monotherapy trial (n=330) of Enlyte, presumably because this FDA-cleared product contains other folate and B vitamins in addition to 7.5 mg of L-methylfolate. Enlyte had a large effect size (0.88) as monotherapy in this clinical trial. The patients had moderate depression, some treatment...
resistant and some not, but all were selected for genetic polymorphisms on the MTHFR gene (C677T or A1298C), making it difficult to compare the results with those of the traditional L-methylfolate studies. In theory, these patients may be more likely to respond to L-methylfolate, but that theory has not been clinically tested, and we do not recommend routine genetic testing before starting L-methylfolate (Mech AW and Farah A, *J Clin Psychiatry* 2016;77(5):668–671).

L-methylfolate is available by prescription or over the counter (eg, Opti-Folate is available as 15 mg tabs for $8/month), while Enlyte is prescription-only ($52/month if not covered by insurance, at www.enlyterx.com).

**CARLAT TAKE**

Coprescribing L-methylfolate may offer a modest boost to antidepressants and is a reasonable choice for patients who want a natural or well-tolerated option. Both standard L-methylfolate and Enlyte are reasonable options.

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### TECHNOLOGY IN PSYCHIATRY

**Can Abstaining From Social Media Help People Feel Better?**

*Michael Posternak, MD.* Dr. Posternak has no financial relationships with companies related to this material.


**STUDY TYPE:** Randomized controlled trial

It has long been speculated that spending too much time on social media might have negative effects on mental health. After all, who wouldn’t get depressed seeing how much fun everyone else in the world seems to be having? Although studies have consistently found a link between excessive social media use and depression, it can be hard to tell whether social media use exacerbates depression or is the result of it.

In this study, researchers recruited 154 volunteers from the community who agreed to be randomized to either continuing social media use as usual or abstaining from it for one week. Facebook, Instagram, Twitter, and TikTok were the four platforms they focused on. The mean age of subjects was 29 years, and subjects spent on average just over one hour a day on social media. Subjects were not required to suffer from a mood or anxiety disorder to participate, although about one-third of the subjects did meet criteria for moderate depression. The main outcomes of interest were reduction in depression and anxiety scores as well as overall sense of well-being.

In order to facilitate abstaining from social media, participants were provided with tips for doing so, such as signing out of relevant social media sites, deleting apps, turning off social media notifications, turning off their phones, and downloading app blockers. Screen time use was monitored using relevant apps.

The first finding of interest is that abstaining from social media is indeed feasible, at least in the short term. Subjects randomized to social media abstinence reduced their screen time use on average from 510 minutes to 21 minutes over the course of the one-week trial. This reduction in social media use was associated with improvements in depression, anxiety, and well-being scores, though the effect on depression was only apparent in those with at least mild depressive symptoms. One limitation of the study is that the subjects who volunteered were likely already motivated to abstain. It remains unknown how realistic abstaining from social media is for most people, or whether it can be maintained much beyond one week.

**CARLAT TAKE**

This study strongly suggests that social media use has detrimental effects on mental health. There are many lifestyle changes, such as increasing exercise, getting adequate sleep, reducing alcohol intake, or cleaning the house, that we routinely recommend to our patients. It may be time to add reducing social media use to that list.

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### BIPOLAR DISORDER

**Marginal Results for Levetiracetam in Mania**

* Kamron Fariba, DO. Dr. Fariba has no financial relationships with companies related to this material.


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

Among the anticonvulsants, a few have passed in mania (carbamazepine, valproate), others have failed (lamotrigine, gabapentin, topiramate), and others remain untested. Levetiracetam (Keppra) is one of those unknowns. It failed in a controlled trial of bipolar depression, and the current study is the first controlled trial to test it in mania.

The investigators randomized 40 outpatients (mean age 40 years) with active mania to receive either levetiracetam plus quetiapine or placebo plus quetiapine. The patients had become noncompliant with their maintenance therapy one to two weeks before the trial began, but they were not specifically treatment resistant. They scored at least 20 (mean of 37) on the 60-point Young Mania Rating Scale (YMRS) and had an average of three to four past manic episodes. Those with a history of rapid cycling or with active suicidal planning or substance use disorders were excluded.

The two medications were started simultaneously as 1) levetiracetam 20 mg/kg/day for four weeks then 50 mg/kg/day for the final two weeks; and 2) quetiapine 100 mg/day for two weeks then 300 mg/day for the final four weeks (below quetiapine’s typical range of 400–800 mg for mania). The primary outcome was the change in YMRS scores over the six-week trial. Secondary measures assessed tolerability along with a specific rating scale for suicidality.

The results were inconclusive. At the six-week mark, which was the primary outcome measure, the percent...
A New Intervention for Shift-Work Disorder

Xavier Preud’homme, MD. Dr. Preud’homme has no financial relationships with companies related to this material.

REVIEW OF: Cheng WJ et al, Sleep 2022;45(4):zsac034

STUDY TYPE: Randomized crossover design

Night shift work is an occupational hazard. One in five shift workers have problems with sleep, attention, and wakefulness that qualify for a diagnosis of shift-work disorder. Management of this disorder involves appropriate timing of light and darkness, but no one has looked at the question of when sleep should occur. This study examined that issue by comparing morning sleep (ie, after the night shift) to evening sleep (ie, before the night shift) in people with shift-work disorder.

Sixty adults were randomized to a morning (9 am–5 pm) or an evening (3–11 pm) sleep schedule for the first week of the intervention, crossing over to the other schedule for the second week (30 in each arm). The average age was 30 years, 80% were women, and 66% worked as night-shift nurses. The diagnosis of shift-work disorder was made with ICSD-3 criteria and confirmed by a 14-day sleep log. Adherence to the protocol was monitored with daily sleep and actigraphy data. No participants used prescribed sleep aids or stimulants during the study period.

The evening sleep protocol resulted in a 30-minute longer duration of sleep (5.3 vs 4.8 hours) as well as improvements in sleep quality and daytime somnolence throughout the week. Attention also improved, but only on the day after the first shift. The evening protocol was particularly effective for subjects with an evening chronotype (eg, “night owls”).

CARLAT TAKE

Ask your patients who work the night shift whether they sleep before or after their shift. If a later sleep schedule is compatible with their social and family life, start a conversation about the potential benefits of sleeping in the later part of the day so they wake about an hour before their shift.

PSYCHOTHERAPY

An End to YAVIS Syndrome?

Sin Yan Lo, PMHNP-BC. Ms. Lo has no financial relationships with companies related to this material.


STUDY TYPE: Systematic review

In 1964, William Schofield coined the term “YAVIS” to describe the ideal psychotherapy patient: “young, attractive, verbal, intelligent, and successful.” But if the conclusions of this new systemic review are correct, we’ve been getting it wrong for over half a century.

This systematic review included 10 meta-analyses looking at predictors of psychotherapy outcomes in depression. All trials in these meta-analyses compared therapy with another form of treatment or control. Each analysis included three to 39 trials (median 12), and each trial involved 482–8,107 patients (median 1,943). Seven of the meta-analyses looked at cognitive behavioral therapy (CBT), and the other three looked at psychodynamic therapy, cognitive behavioral analysis system of psychotherapy, and internet-based prevention programs. The systematic review identified predictors and moderators for each meta-analysis and integrated the results in a narrative form. Some of the trials were included in more than one meta-analysis, and the authors did not adjust for this duplication of data.

Six of the meta-analyses concluded that therapy was more effective when patients had a higher severity of depression (measured by clinical interview or rating scales). Two found that older individuals benefited more from therapy for depression. Gender, education level, and relationship status did not seem to make a difference, but no other predictors were examined, which is one limitation of this review. Additional limitations include the lack of long-term outcomes and the overrepresentation of CBT.

Both of these findings are a challenge to conventional wisdom. The American Psychiatric Association gives psychotherapy a higher level of recommendation for mild to moderate depression than severe depression in their 2010 Practice Guidelines. YAVIS emphasizes youth and attractiveness, a paradigm that seems more rooted in outdated biases than empirical evidence.

CARLAT TAKE

Contrary to common beliefs, older and more severe illness predicted psychotherapy response among patients with depression in this large analysis.
When Shorter Is Better
Continued from page 4

1. Set up the expectation of a short-term trial from the start.
2. Pair the treatment with behavioral changes that can prevent relapse, such as exercise or psychotherapy. Start hypnotics with a behavioral program like CBT for insomnia, which is available through self-guided apps like Somryst or CBT-i Coach (see TCPR March 2022).
3. Taper the medication slowly, over at least two weeks, and preferably longer for medications with known withdrawal problems like lithium, benzodiazepines, and serotonergic antidepressants.

Evidenced by a law degree from Yale, a tenured professorship at the University of Southern California, and a MacArthur Foundation fellowship (I’d be thrilled with any one of those!). Furthermore, she developed and maintained strong, mutually engaging social connections. In considering her trajectory, it is important to note she doesn’t seem to suffer significant negative symptoms of schizophrenia (for those who doubt, she shows her expressiveness in her TED Talk titled “A Tale of Mental Illness—From the Inside”). Some readers may even think she was misdiagnosed. In the final chapter, she presents a smart defense of her diagnosis.

The paradox of her condition might best be summed up with this vignette: Before her wedding to a man she loved, she asked a dear friend from law school, “Will aliens be attending the reception?” She was not joking.

For those interested in purchasing the book, visit www.hachettebooks.com.

—Edmund S. Higgins, MD. Affiliate Associate Professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina. Emily S. Whisler, DO. Child & Adult Psychiatry Fellow, Stanford University School of Medicine. The authors have no financial relationships with companies related to this material.
CME Post-Test

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1. In a study by Babyak and colleagues, how did the response to sertraline differ from aerobic exercise in major depression (LO #1)?
   [ ] a. Sertraline was more effective than exercise in the short term
   [ ] b. Exercise was more effective than sertraline in the short term
   [ ] c. Exercise and sertraline had similar effects over the short and long term
   [ ] d. Exercise and sertraline had similar effects in the short term, but exercise was more effective over the long term

2. Which of the following is a modifiable risk factor for torsades de pointes (LO #2)?
   [ ] a. Metabolizer status
   [ ] b. Bradycardia
   [ ] c. Structural or functional heart disease
   [ ] d. History of QT prolongation

3. In a sleep study by Yamasato and colleagues, what kind of music was chosen as relaxing by more than 75% of participants in the preferred music group (LO #3)?
   [ ] a. Classical
   [ ] b. Gregorian chant
   [ ] c. Popular
   [ ] d. Ambient

4. In a systematic review of adjunctive antidepressants for acute bipolar depression, mood switching occurred in ____ of participants (LO #4).
   [ ] a. 12%
   [ ] b. 10%
   [ ] c. 8%
   [ ] d. 5%

5. Patients with nonrecurrent depression can be tapered off an antidepressant after three months of recovery (LO #1).
   [ ] a. True
   [ ] b. False

6. Which of the following has been associated with the risk of QT prolongation at therapeutic doses (LO #2)?
   [ ] a. Bupropion
   [ ] b. Citalopram
   [ ] c. Mirtazapine
   [ ] d. Sertraline

7. Involuntary musical imagery (earworms) is one of the downsides to music therapy (LO #3).
   [ ] a. True
   [ ] b. False

8. In a review of findings from three trials on L-methylfolate, which of the following dosages had a moderate treatment effect (LO #4)?
   [ ] a. 21 mg/day
   [ ] b. 15 mg/day
   [ ] c. 10 mg/day
   [ ] d. 7.5 mg/day
Music for Sleep — Continued from page 6

that listening to music regularly was associated with “involuntary musical imagery,” aka earworms, as well as a 54% worsening of PSQI when the earworms occurred at night. Female sex and instrumental music were more associated with earworms (Scullin MK et al, Psychol Science 2021;32(7):985–997).

The heterogeneity of subjects, methods, and mechanisms linking bedtime music and improved sleep indicate that music is a flexible and helpful intervention for patients with mild to moderate insomnia. For most, slow, relaxing music produces the best effects. Today’s digital music players have sleep timers that can turn the music off after a set time period. Based on the results above, patients could start by setting a timer for 45 minutes, but those who struggle with middle-of-the-night awakenings may want to keep music accessible from bed. Patients who don’t respond to music or have more severe insomnia may need CBT-I or hypnotics.

Music improves subjective complaints of insomnia. It is safer than sleep medication, and a healthy alternative to sleeping with the TV on.

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