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Chris Aiken, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Lifestyle Interventions

Learning Objectives

After reading these articles, you should be able to:

1. Tailor treatments based on individual factors in antidepressant augmentation.
2. Employ the key principles of lifestyle medicine and their role in preventing chronic diseases.
3. Summarize some of the current research findings on psychiatric treatment.

A Personalized Approach to Antidepressant Augmentation

Deepti Anbarasan, MD. Associate Professor, Psychiatry and Neurology, New York University, New York, NY. David Liebers, MD. Psychiatry resident at NYU Langone Department of Psychiatry.

The authors have no financial relationships with companies related to this material.

Highlights From This Issue

On the cover. Personalized augmentation strategies for depression include mirtazapine for anxious features, nimodipine for vascular depression, lithium for suicidality, and lurasidone for mixed features.

Q&A on page 1. Dr. Beth Frates shows us how to engage patients toward the six pillars of a healthy lifestyle.

Research update on page 6. Transcranial direct current stimulation (tDCS) shows promise in ADHD.

Personalized medicine aims to match each patient with a treatment that uniquely fits their symptoms, biological markers, or other features like age and gender. It is only recently that we have research to guide us in this direction. In this article, we'll look at ways to personalize the approach to antidepressant augmentation.

Anxious depression

When it comes to antidepressant augmentation, mirtazapine sits on the fence. Several large randomized controlled trials (RCTs) were negative, but a meta-analysis that included small but positive trials found an encouraging signal. This popular augmentation strategy may be most successful with a personalized approach. A signal in anxiety

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Q&A With the Expert

Lifestyle Medicine in Psychiatry
Beth Frates, MD

Part-time Clinical Assistant Professor, Harvard Medical School Physical Medicine and Rehabilitation.

Dr. Frates reports she is on the boards of Jenny Craig, obVus Solutions, and Clearning.com. Dr. Aiken has reviewed this educational activity and has determined that there is no commercial bias as a result of this financial relationship.

TCPR: What is lifestyle medicine?

Dr. Frates: Lifestyle medicine is a specialty that focuses on the lifestyle causes of chronic diseases, such as cardiovascular disease, diabetes, obesity, metabolic syndrome, and psychiatric disorders like depression (www.lifestylemedicine.org). We do this through six pillars:

1) Routine physical activity
2) A whole-food, plant-predominant eating pattern
3) Restorative sleep
4) Stress resiliency
5) Positive social connection
6) Avoidance of risky substances

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A Personalized Approach to Antidepressant Augmentation

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reduction in one of those RCTs prompted a second look at the evidence, which revealed benefits in both depression and anxiety among those with severe anxiety at baseline (number needed to treat [NNT]=5 for response) (Rifkin-Zybutz R et al, *J Psychopharmacol Oxf Engl* 2020;34(12):1342–1349). You could consider mirtazapine augmentation in anxious depression, as well as in depression with insomnia.

Quetiapine worked in augmentation for both anxious and depressive symptoms in two RCTs of major depression with comorbid anxiety disorders (average dose 200 mg QHS). This antipsychotic has a large effect in generalized anxiety disorder (GAD), and nearly earned FDA approval in GAD but for a drawback that also gives us pause—like other antipsychotics, quetiapine has serious side effects and should be reserved for severe anxiety.

Depression with suicidality

Lithium, along with clozapine and the ketamine formulations (ketamine and esketamine), is one of the only psychotropics with robust antisuicide effects. A couple of recent studies, however, have cast doubt on lithium's antisuicide effects. One of these studies was a meta-analysis that excluded important older studies and instead focused on more recent, shorter studies that were likely not large or long enough to detect the relevant effect (Nabi Z et al, *Epidemiol Psychiatr Sci* 2022;16;31:e65). The other was an RCT that only looked at suicidal behaviors and attempts rather than death by suicide (Katz IR et al, *JAMA Psychiatry* 2022;79(1):24–32).

Rather than overturn the evidence that lithium reduces suicide risk, these studies helped to underscore that observing lithium's antisuicide effect requires longer follow-up, and that lithium may not reduce all suicidal behaviors. In fact, decades of prospective and observational data support lithium's role in patients with depression and suicidality. Lithium use requires monitoring of thyroid (10%–15% lifetime risk of hypothyroidism) and renal function. For depression augmentation, we start at 150–300 mg daily and titrate slowly every five days, aiming for a level between 0.6–0.8 mEq/L. The response takes two to six weeks.

Intranasal esketamine has emerged as another augmentation approach for suicidal patients. One common dosing practice is administering 84 mg twice a week for four weeks. The differentiator with esketamine (much like ketamine) is the speed of action—it works within hours, even faster than ECT (Ionescu DF et al, *Int J Neuropsychopharmacol* 2021;24(1):22–31). But just how long to continue treatment is still largely an open question. IV ketamine may work just as well with effects seen even after a single dose.

Depression with insomnia

Dozens of trials of benzodiazepines in augmentation of antidepressants and monotherapy have established their role not just in improving sleep, but in addressing certain core symptoms of depression. Most of these studies focused on relatively short-term use, and the benefits need to be weighed against known risks of long-term benzodiazepine therapy (eg, dependence, falls, cognitive impairment). The same antidepressant effect has not held up with most z-hypnotics, with the exception of eszopiclone (Lunesta). In two RCTs, eszopiclone 3 mg improved depressive symptoms even when sleep items were removed from the analysis (NNT=11 for remission) (Fava M et al, *Biol Psychiatry* 2006;59(11):1052–1160; McCall WV et al, *J Clin Sleep Med* 2010;6(4):322–329). Later controlled trials found benefits in GAD and chronic pain with eszopiclone.

Alternatively, some antidepressants like mirtazapine, trazodone, and quetiapine have evidence to improve sleep quality and initiation.

Depression with mixed features

Depression with mixed features is a newer specifier in the DSM-5, and it is used for patients who have depressed mood combined with at least three manic symptoms but do not have enough manic symptoms to meet criteria for bipolar disorder. These patients present as wired, restless, and irritable. In these patients, lurasidone is a good choice as it has robust evidence as monotherapy for mixed features. Aripiprazole is also a good choice as it worked as augmentation in depression with mixed features in a large

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A Personalized Approach to Antidepressant Augmentation

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VA trial (Zisook S et al, *Am J Psychiatry* 2019;176(5):348–357). Surprisingly, that trial also pointed to bupropion augmentation as a preferential treatment for mixed features. Among the antidepressants, bupropion has the lowest risk of inducing manic symptoms.

In some patients, antidepressants may cause mixed symptoms to emerge. If the timeline of mixed symptoms suggests this might be the case for your patient, for more rapid relief, it makes sense to augment with an antipsychotic like lurasidone while slowly tapering the antidepressant.

Winter depression

Light therapy has a medium effect size in winter depression, a common depressive subtype that affects up to 20% of people with major depressive disorder (MDD) (see "A Practical Guide to Light Therapy" in the November/December 2019 issue of *TCPR*). For full effect, the light needs to be white spectrum, ideally 10,000 lux, and should be used just after waking up, before 8 am. The best light boxes are at least 12 x 17 inches and should be angled at 30 degrees over the patient's head for 30–60 minutes per day. Patients note some improvement within one to two weeks.

Vascular depression

Microvascular infarcts accumulate in the brain as vascular disease progresses, and this is speculated to be a common cause of depression in older adults. After age 50, one in five patients with depression have a vascular contribution, and this rises to one in two after age 65 and nearly 100% by age 75 (Taylor WD et al, *Am J Psychiatry* 2018;175(12):1169–1175). Patients with heart disease, diabetes, and hypertension are particularly at risk. Confirmation is found through white matter abnormalities in a brain MRI, even if patients are described as "normal for age."

Antidepressant efficacy is greatly reduced in this condition, so augmentation is often necessary. One strategy is using nimodipine, an antihypertensive that improves cerebral blood flow and showed efficacy in two RCTs of vascular depression (remission NNT=5 and NNT=4) (Taragano FE et al, *Int J Geriatr Psychiatry* 2001;16(3):254–260; Taragano FE et al, *Int Psychogeriatr* 2005;17(3):487–498). The target dose is 90 mg TID, and it takes up to two months to see an effect. Start at 15 mg TID for patients who are already on blood pressure medicine, or 30 mg TID for other patients, and raise by 15 mg every 10 days.

Repetitive transcranial magnetic stimulation (rTMS) is another option for vascular depression. In one study, rTMS brought remission with an NNT of 5 (Jorge RE et al, *Arch Gen Psychiatry* 2008;65(3):268–276).

Inflammation and obesity

Inflammation, obesity, and depression are closely linked. A growing body of evidence points to specific antidepressant strategies for patients who are obese (BMI >30) or have inflammation, as measured by high-sensitivity C-reactive protein (hs-CRP ≥3).

Two augmentation strategies may be specifically effective in patients with both obesity and inflammation: L-methylfolate (15 mg/day) and bupropion (300 mg/day). Both worked preferentially in those populations in large RCTs (Shelton RC et al, *J Clin Psychiatry* 2015;76(12):1635–1641). Omega-3 fatty acids also may be effective in patients with elevated inflammatory markers (hs-CRP ≥3). They are usually dosed as 1,000–3,000 mg/day of combined EPA and DHA omega-3s, with the EPA ratio at least twice the DHA amount. However, higher doses (EPA >4,000 mg/day) were more effective in patients with obesity and inflammation in a recent study (Mischoulon D et al, *J Clin Psychiatry* 2022;83(5):21m14074).

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Augmentation Strategies for Depression Based on Clinical Features and Comorbidities

Feature	Augmentation Agent (target dose/level)	Notes
Anxious depression	Mirtazapine (30–45 mg/day) Quetiapine (200–300 mg/day)	
Fatigue	Modafinil (100–200 mg/day) Armodafinil (150–250 mg/day)	
Inflammatory state	L-methylfolate (15 mg/day) Minocycline (200 mg/day) Omega-3 fatty acids (up to 4 g/day) N-acetylcysteine (1800 mg/day)	Inflammation defined as hs-CRP ≥3; for omega-3 fatty acids, EPA:DHA should be >2:1
Insomnia	Eszopiclone (3 mg/night)	
Insulin resistance	Pioglitazone (30 mg/day)	Fasting glucose >100 mg/dL or oral glucose tolerance at 120 min >140 mg/dL
Mixed features	Lurasidone (20–60 mg/day) Aripiprazole (5–10 mg/day) Bupropion (300–400 mg/day)	
Obesity	L-methylfolate (15 mg/day) Omega-3 fatty acids (up to 4 g/day)	BMI >30
Psychosis	ECT Antipsychotics	
Suicidality	Lithium (0.6–0.8 mEq/L) Intranasal esketamine	
Vascular depression	Nimodipine (90 mg TID) rTMS	
Winter depression	Light therapy	10,000 lux; 12 x 17 inches; 30–60 min in early morning

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Augmentation options with unique benefits in patients with inflammation include N-acetylcysteine and minocycline (Porcu M et al, *Psychiatry Res* 2018;263:268–274).

Insulin resistance and depression

Patients with depression and diabetes may benefit from augmentation with the antidiabetic medication pioglitazone. The research is preliminary, with one trial showing general benefits in MDD and another showing improvement only in those with insulin resistance (Lin KW et al, *Psychiatry Res* 2015;230(3):846–852). We recommend restricting pioglitazone to patients with comorbid diabetes and using it in consultation with their PCP (start 15 mg/day, target 30 mg/day). Pioglitazone is well tolerated but carries a black box warning about a small increased risk of bladder cancer.

Psychotic depression

For the psychotic subtype, ECT is the gold standard, bringing over 90% of cases to remission. If medication therapy is used, antipsychotic augmentation is usually necessary, but doses need to be higher than those used for general augmentation of MDD without psychosis (Farahani A and Correll CU, *J Clin Psychiatry* 2012;73(4):486–496). The STOP-PD II trial suggested that continuing the antipsychotic for six months reduces the risk of relapse (Flint AJ et al, *JAMA* 2019;322(7):622–631).

Depression with fatigue

Augmentation with modafinil has a limited role in treatment-resistant depression (NNT=10 for remission), but it might be useful for targeting residual fatigue. Modafinil (100–200 mg/day) and its isomeric cousin armodafinil (150–250 mg/day) are well tolerated and may boost overall adherence, as patients cite fatigue as a leading reason for antidepressant discontinuation.

For an overview of all the medications discussed here, see the table on page 3.

CARLAT VERDICT

There are many types of depression, and specific signs and symptoms can point the way toward a more personalized augmentation strategy.

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Expert Interview

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Through these pillars, we can manage, treat, and in some cases even reverse chronic conditions. *(Editor's note: See the table "Six Lifestyle Pillars: Target Doses."*)

TCPR: How are those pillars relevant in psychiatry?

Dr. Frates: We have the most data in depression, and a recent study from the UK Biobank illustrates the relevance of the pillars very well. The authors looked at how lifestyle influenced the risk of depression over nine years in 287,282 people. The lifestyle factors they arrived at are very close to the six pillars, but what is interesting is that sleep rose to the top. A healthy sleep duration of seven to nine hours decreased the risk of depression by 22%. The other factors were social connection, regular physical activity, low to moderate sedentary activity, healthy diet, never smoking, and moderate alcohol consumption. People could lower their risk of depression by 72% by having all these factors in place. By comparison, good genes reduced the risk by 25% (Zhao Y et al, *Nat Mental Health* 2023;1:736–750).

TCPR: Could the causation go the other way, though? I mean, people with genetic risk for depression may also be prone to unhealthy lifestyle, and perhaps they would have developed depression independent of lifestyle.

Dr. Frates: Yes, this was not a randomized trial, so that is possible. The authors did use a technique called Mendelian randomization to control for influence of genes, however, and we do have other studies that have tested out the pillars as truly randomized interventions for depression. Some have brought all the pillars together in a group lifestyle modification program, but most have tested them individually (Aguilar-Latorre A et al, *Front Med (Lausanne)* 2022;9:954644). Three studies tested a Mediterranean-style diet and several dozen tested aerobic exercise. For example, the SMILE trial compared exercise to an antidepressant (sertraline 50–200 mg/day) over four months. At the end, both interventions had similar effects on depression, and both worked better than a placebo pill. The dose of exercise was 45 minutes of physical activity three days a week, and the authors randomized people to do it on their own or in a supervised setting—there was little difference between the two (Blumenthal JA et al, *Psychosom Med* 2007;69(7):587–596).

TCPR: How does exercise change the brain?

Dr. Frates: It's not just postexercise endorphins that make us feel good. Exercise modulates dopamine, serotonin, and norepinephrine. After an aerobic run, there is a measurable increase in brain-derived neurotropic factor

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Six Lifestyle Pillars: Target Doses

Physical Activity	Weekly doses: 150–300 minutes of moderate-intensity physical activity (something that raises the heart rate and breaks a sweat, eg, brisk walking) or 75–150 minutes of vigorous physical activity (something that makes it difficult to talk, eg, jogging)
Diet	Mediterranean-style, plant-forward diet such as the Harvard Healthy Plate (1/2 plate is fruits and vegetables, 1/4 is whole grains, 1/4 is healthy proteins like fish, lean meats, nuts, or beans); avoid saturated fats and fried, processed, sugary, or fast foods
Sleep	Seven to nine hours of restorative sleep per night
Stress Resiliency	Regular practice of a technique like mindfulness, gratitude, yoga, or tai chi 5–20 minutes per day
Social Connection	Connect with someone you have a quality relationship with at least once per day
Substance Use	If you don't drink alcohol, don't start; if you do drink, limit yourself to one standard drink every other day and drink three glasses of water for every glass of alcohol; if you smoke, quit

Expert Interview
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and—down the road—an increase in hippocampal volume. Exercise also has cognitive benefits that antidepressants do not. It helps consolidate memories.

TCPR: What do we know about lifestyle and anxiety?

Dr. Frates: Compared to depression, the studies we have for anxiety are less rigorous and less conclusive. The best we can say is that exercise, diet, and behavioral interventions for sleep might reduce anxiety, but it's not definitive (Stonerock GL et al, *Prog Cardiovasc Dis* 2023;S0033-0620(23)00054-3; Aucoin M et al, *Nutrients* 2021;13(12):4418).

TCPR: How do you work with patients on these pillars? Let's start with sleep.

Dr. Frates: Make the room like a cave—that is, dark and cool. A drop in core body temperature is a signal for sleep, and I recommend a room temperature between 60 and 70 degrees (67 degrees seems to be the sweet spot, but this has to be personalized). For darkness, use blackout curtains or an eye mask to enable a deep sleep for seven to nine hours each night. Dim the lights and shut down computers and screens two to three hours before bed to reduce blue light, which is the wavelength that blocks melatonin release. If screen use before bed is unavoidable, there are computer apps to reduce blue light (eg, f.lux for Windows, Candlelight for Mac), smartphone settings (Nightshift or Twilight mode), and blue light–blocking glasses. Wearing these glasses two to three hours before bed improved insomnia and sleep quality in a few small controlled trials (Janků K et al, *Chronobiol Int* 2020;37(2):248–259). *(Editor's note: The glasses in these studies blocked 65% or more of blue light and can be found in Uvex Skyper or Ultraspec models or at www.lowbluelights.com.)* Stay on a regular schedule and get sunlight in the early morning to set circadian rhythm. Patients who live in a noisy neighborhood should use ear plugs or a white noise machine.

"I start with empathy. 'How did it go? How was your week? Were you able to call your friends?' Indeed, most people are interested in joining a walking group."

Beth Frates, MD

TCPR: What about caffeine?

Dr. Frates: Caffeine binds to the same receptor as adenosine, which is one of the chemicals that helps us fall asleep. It runs the "sleep drive," which is one of the two physiologic forces that regulate sleep. The other force, circadian rhythm, is circular and is driven by light and darkness. Sleep drive is linear—the longer we stay awake, the more adenosine rises. Adenosine builds up throughout the course of the day and usually peaks around 11 pm. Caffeine blocks this effect, and its half-life is four to six hours, so drinking a cup of coffee at 6 pm means half of it is still in the system at bedtime (Frates B, *Am J Lifestyle Med* 2023;17(2):216–218).

TCPR: What about alcohol?

Dr. Frates: Alcohol disrupts sleep. A lot of people use it to fall asleep, but the data show that it actually disrupts sleep.

TCPR: Most patients are more concerned with whether they fall asleep than with the quality of that sleep. How do you change the conversation?

Dr. Frates: This is particularly difficult for people with anxiety and depression, who often have racing, ruminative thoughts that keep them up at night. Lying awake for 10 minutes can feel like an eternity. What I recommend is for them to write down the worries they have, put them on a list, then put the list aside and focus the brain on something else. One suggestion is gratitude—thinking about things the patient is grateful for and trying to name as many as possible. I also get them to focus on their breath.

TCPR: How do you do that?

Dr. Frates: Focusing on the breath is a skill that requires practice. If other thoughts come in, patients can treat those thoughts as a gentle reminder to return focus to the breath. There are several breathing techniques patients can use, and I like to give them options. One is 4-7-8 breathing: Breathe in for a count of 4, hold for a count of 7, and exhale for a count of 8. Another is boxed breathing: Breathe in for a count of 4, hold for a count of 4, and exhale for a count of 4. Some patients find boxed breathing easier to remember than 4-7-8. The key is to practice the techniques with them in the room.

TCPR: You gave us targets for the six pillars. How do you work those in with patients?

Dr. Frates: I am collaborative, not prescriptive. I don't say to patients "You need to exercise 150 minutes every week." Instead, I start by being curious, so I'll say "Tell me about what you do right now with movement." A lot of people don't like the term "exercise," so calling it physical activity or movement is an option. "How does that movement impact you? How do you feel after you walk your dog in the morning?" Usually they respond with positive experiences, and I follow up with "Well, what would you like to do with it moving forward? Do you know about the guidelines?" Then I ask permission to share the research. "Would you like to hear about some fascinating research I just found from the UK Biobank?" And I share it and ask what they think. Another possibility is to focus on the sedentary behavior. "Do you want to talk about sitting and sitting disease?"

TCPR: That sounds like a more empathic approach.

Dr. Frates: I start with empathy. When I put my coach hat on, I'm curious, open, and nonjudgmental. There is no shame, blame, or guilt in the room. I'm appreciative of the person in front of me, what they bring as their own strengths. If they've already made some movement, any movement, toward a healthy pattern, terrific. I am compassionate with that empathy. Finally, I'm always honest. That's my coach hat.

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Research Updates IN PSYCHIATRY

NEUROMODULATION

Powering Up the Brain: tDCS for ADHD?

Jesse Koskey, MD. Dr. Koskey has no financial relationships with companies related to this material.

REVIEW OF: Teixeira Leffa D et al, *JAMA Psychiatry* 2022;79(9):847–856

TYPE OF STUDY: Randomized double-blind sham-controlled trial

Does wearing a cap powered by less than 1% the juice of a nine-volt battery actually do anything? Transcranial direct current stimulation (tDCS) delivers a weak electrical charge to the scalp, and patients are increasingly using this device on their own, inspired by small but promising studies in depression. This study assessed its effects in ADHD.

The researchers randomized 64 adults with moderate to severe inattentive symptoms of ADHD to either daily tDCS or sham therapy for 28 days. The subjects stopped stimulants 30 days before the study, and none of them were taking other ADHD medications during the study. The subjects had no significant psychiatric comorbidities. Their average age was 38, and women were overrepresented in the treatment arm (60% vs 35%). The primary outcome was self-reported inattention at weeks zero, two, and four. The study was carried out in Brazil and all subjects were of European descent. The research was grant-funded, although three of the authors received royalties from their patents on the tDCS devices used.

tDCS was delivered over both dorsolateral prefrontal cortices as a 2 mA current through a cap for 30 minutes. The sham cap mimicked the feeling of tDCS.

Using an intention-to-treat analysis, the researchers found that tDCS reduced self-reported ADHD symptoms by week four, with a large effect size of 1.23 (95% confidence interval 0.67–1.78). More patients guessed they were in the treatment arm than would be predicted by chance. A total of seven active and two control-group participants dropped out for various reasons, including dizziness and depression in the tDCS group. Only mild side effects were reported, and they were consistent with other tDCS research. Skin tingling or redness, scalp burning or pain, headache, and mood changes were the most common. The tDCS group completed an average of 20 sessions versus 24 in the sham group.

CARLAT TAKE

Despite the positive findings for tDCS in ADHD, we'll wait for replication. The small size, financial bias, and risks of unblinding give us pause.

Do Mood Stabilizers Prevent Death in Bipolar Disorder?

Alex Evans, PharmD, MBA. Dr. Evans has no financial relationships with companies related to this material.

REVIEW OF: Chen PH et al, *Acta Psychiatr Scand* 2023;147(3):234–247

STUDY TYPE: Retrospective cohort study

The mortality rate in bipolar disorder is approximately double that of the general population. While suicide is one reason, bipolar disorder increases the risk of death from natural causes, too. Rates of suicide and all-cause mortality are lower with lithium, and this study compared those rates with anticonvulsant mood stabilizers (valproic acid, lamotrigine, and carbamazepine). Antipsychotics were not included.

Researchers analyzed records from 25,787 patients who were hospitalized for bipolar disorder (bipolar I, II, and not otherwise specified) in Taiwan using a national insurance database. Exposure to mood stabilizers was measured for five years following hospitalization. Sixteen percent of the patients died during the study period.

The primary outcome was the rates of suicide, all-cause mortality, and natural mortality. These rates were presented as standardized mortality ratios (SMRs). This is a comparison of the observed rate of death to that expected in the general population, where an SMR above 1 indicates a higher risk of death. SMRs were controlled for sex, age, employment status, comorbidities, and concomitant drugs.

For bipolar disorder, the SMRs were 26.0 for suicide, 5.3 for all-cause mortality, and 4.7 for natural mortality. The risk of suicide was highest in those age 45–65 years and in those with multiple psychiatric comorbidities.

Mood stabilizer use was associated with lower risks of suicide, all-cause mortality, and natural mortality, with adjusted hazard ratios (aHR) of 0.55–0.60. Lithium had the most profound effects, with an aHR for each outcome of 0.37–0.39. There was a strong association between higher cumulative lithium doses, longer lithium exposure, and a reduced risk of death from any cause.

Valproic acid also had an association with lower mortality, but it was not as impressive as that of lithium. Lamotrigine and carbamazepine had no significant association with either higher or lower mortality rates.

All of the study participants had at least one hospitalization, which may have led to an overestimation of the risks seen in this study.

CARLAT TAKE

Patients who took lithium lived longer than those on anticonvulsants or no treatment, with a lower risk of death from suicide as well as natural causes. These data put lithium's medical risks—including renal impairment, hypothyroidism, and toxicity—in perspective and argue against the trend toward decreased lithium utilization that we've seen since the introduction of branded options in the 1990s.

CME Post-Test

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1. Which antidepressant augmentation strategy was not effective overall but showed a signal of efficacy in anxious depression (LO #1)?
   - [ ] a. L-methylfolate
   - [ ] b. Lithium
   - [ ] c. Modafinil
   - [ ] d. Mirtazapine

2. Which is NOT one of the pillars of lifestyle medicine (LO #2)?
   - [ ] a. Routine physical activity
   - [ ] b. Stress resiliency
   - [ ] c. Pursuit of learning
   - [ ] d. Avoidance of risky substances

3. Which intervention reduced self-reported symptoms of ADHD with an effect size of 1.23 in a recent study (LO #3)?
   - [ ] a. Transcranial magnetic stimulation
   - [ ] b. Alpha-stimulation
   - [ ] c. Transcranial direct current stimulation
   - [ ] d. Biofeedback

4. Which medication has evidence to augment antidepressants in patients with insomnia and depression (LO #1)?
   - [ ] a. L-methylfolate
   - [ ] b. Eszopiclone
   - [ ] c. Lithium
   - [ ] d. Modafinil

5. In the UK Biobank study, which lifestyle factor had the greatest effect on reducing the risk of depression (LO #2)?
   - [ ] a. Regular physical activity
   - [ ] b. A healthy diet
   - [ ] c. Positive social connection
   - [ ] d. Restorative sleep

Expert Interview

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TCPR: And if they don't have progress?

Dr. Frates: If they say "I don't do anything. I am way too busy. I have two jobs. I'm going through divorce and raising teenagers!" I'm not going to respond with "Well, if you did do exercise, your mood would increase and you'd be less likely to have depression." Clearly they're not ready to talk about it. If, however, there is an opening, I'll say "You are going through a lot. What do you think would help at this time in your life?" They might say "I'd be a different person if I could just sleep." I'll be open, curious, and ready to follow their lead. I'll say "What motivates you to want to feel better, to want to change?" They'll probably respond with something like "Well, my kids need me." I'll empathize and ask what they think they need to do to be there for their kids. This will likely result in a statement like "I need sleep. I need energy, so I need to exercise more."

TCPR: What comes next?

Dr. Frates: Next we go to building confidence. The patient is motivated to change but doesn't feel confident that they can. If I ask what's holding them back, they might say "I've tried all these different apps and exercise classes and nothing works. Back in the day, I used to walk, but I can't walk anymore." I'll focus on the evidence that a new pattern is possible and say something like "Tell me about the time when you were walking. What were you doing?" They might share that they used to have a routine where they met with friends to walk after dinner, for example, but having kids made sticking to the routine difficult. I'll reflect on this and suggest options. For example, I might say "It sounds like social connection helped you stay motivated. I wonder if there is a way you could do that now. Could you walk with your kids? Could you walk with people in the neighborhood after dinner?"

TCPR: How do you wrap that up?

Dr. Frates: After I've started with empathy, aligned motivation, and built confidence, next is making a SMART goal, which means making a goal that is **S**pecific, **M**easurable, **A**ction-oriented, **R**ealistic, and **T**ime-bound. I'll ask

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"What could you realistically start with this week?" The patient might say "Well, two of my neighbors are trying to lose weight, so I bet they're going to want to walk with me." Now I leverage that information to make the goal specific. "Which day are you going to call them? What are you going to say?" Once we have the details down, we set up accountability. Hopefully, the patient has a buddy who can check up on this goal, or it could be me as the provider at the next visit.

TCPR: How do you check in on their progress?

Dr. Frates: I like to meet with them every week. I start with empathy. "How did it go? How was your week? Were you able to call your friends?" They may say "Yes, and they're really interested." Indeed, most people are interested in joining a walking group. I'll ask "How is that working for you? How is your mood and energy?" I connect this inquiry with their motivator by asking "How are you feeling with your teenagers?" I keep following that empathy and aligning with the values that motivate them.

TCPR: Do you have patients track their progress?

Dr. Frates: That is part of accountability. For movement, some people use actigraphy—step counters—through their cell phone or wearable devices. Some like pen-and-paper logs. All of this work has to be personalized.

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

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