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Chris Aiken, MD
Editor-in-Chief

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Mind-Gut Connection

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Learning Objectives

After reading these articles, you should be able to:

1. Identify the benefits and drawbacks of lamotrigine.
2. Describe the relationship between gut microbiota and mental health.
3. Summarize some of the current research findings on psychiatric treatment.

How to Use Lamotrigine

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

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

Highlights From This Issue

Dr. Dinan brings us up to date on the link between depression and the gut microbiome, and whether probiotics or lifestyle change is the best way to address microbiome health.

Lamotrigine is not FDA approved for acute bipolar depression, but new studies suggest it may have a role there, as well as in a host of comorbidities common to bipolar disorder.

The benzo-dementia link is called into question, but the beta blocker–depression link garners more support.

Lamotrigine is FDA approved as maintenance treatment for bipolar disorder—that is, for delaying episodes of depression, hypomania, or mania. However, it is not approved for active depression or mania—which has given it a reputation as a "light" mood stabilizer. For patients who appreciate tolerability, that's a good thing, but it isn't the first choice when rapid action is needed. In this article I'll clarify who is most likely to respond to lamotrigine and how to optimize its effects.

When to use it

Lamotrigine's main use is for prevention, and it's better at preventing bipolar's depressive phases than its manic phases. That profile makes it a good choice for patients with bipolar II, who—on average—spend half their lives in

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Q&A With the Expert

Probiotics in Psychiatry
Ted Dinan, MD, PhD

Professor of psychiatry at University College Cork, Ireland. Dr. Dinan's research focuses on depression, irritable bowel syndrome, and the influence of the gut microbiota on brain function. He has published over 500 scientific papers and numerous books, including 2019's The Psychobiotic Revolution.

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

TCPR: What is the gut microbiome?

Dr. Dinan: It is the collection of microorganisms within the intestine. It functions like a separate organ and is about the same weight as an adult brain. Mainly it's made up of bacteria, which is where our research has focused, but there are viruses and fungi in there as well. The traditional view was that these organisms are along for the ride—we feed them, and they don't do us any harm. In the last 15 years we've realized that the relationship is more complicated and—when it goes well—symbiotic. We feed them, and they in turn produce chemicals that the brain and body require.

TCPR: How do these bacteria influence the brain?

Dr. Dinan: Much of the communication is through the vagus nerve, which sends signals from the brain to the gut and vice versa. In 2011 we showed that certain microbes can no longer communicate with the brain if the vagus

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How to Use Lamotrigine
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depression and 4% in hypomanic or mixed states (Terao T et al, *J Clin Psychiatry* 2017;78(8):e1000–e1005). In bipolar II, lamotrigine can be used as monotherapy or augmentation, but in bipolar I, it's best reserved for augmentation because it does not treat mania and is not very good at preventing it.

Lamotrigine's main drawback is that it is slow to act, which has led to some confusion about whether it works in acute depression.

A checkered history in bipolar depression

Lamotrigine got off to a rough start in the late 1990s when four out of five manufacturer-supported trials failed to show efficacy in acute bipolar depression. Later, two large studies—which were not manufacturer supported—found that it did treat acute depression. So, what happened?

The early, failed studies were monotherapy trials, while the positive studies used lamotrigine as augmentation. But more importantly, the negative studies were shorter, lasting 7 weeks, while the positive trials lasted 8–12 weeks. Lamotrigine has a slow build, taking 4–6 weeks to reach a therapeutic dose. It starts to separate from placebo at 6–7 weeks, and its benefits plateau around 10–21 weeks. At 7 weeks, it's about half as effective as an atypical antipsychotic, and after a few months its efficacy is similar to an atypical (van der Loos MLM et al, *Acta Psychiatr Scand* 2010;122(3):246–254; Geddes JR et al, *Lancet Psychiatry* 2016;3(1):31–39).

In practice, one way around this delay is to start with an antipsychotic for bipolar depression (eg, cariprazine, lurasidone, olanzapine-fluoxetine combo, or quetiapine) and then add lamotrigine as the patient starts to recover. After 6 months of steady recovery, the antipsychotic can be slowly tapered off over 1–2 months (see *TCPR* Jan 2020, "Antipsychotic Maintenance: How Long Is Enough?").

Other uses

In bipolar disorder, lamotrigine works well in patients with ultra-rapid mood swings that change on a daily or weekly basis, including cyclothymic disorder. In a placebo-controlled study, lamotrigine reduced those ultra-rapid mood swings by 50% (Goldberg JF et al, *Biol Psychiatry* 2008;63(1):125–130).

Outside of bipolar disorder, lamotrigine might have a role in borderline personality disorder, obsessive-compulsive disorder, and depersonalization disorder. It's supported by one or two small controlled trials in each of those disorders (dose range 100–200 mg/day). There was a recent negative trial in borderline personality disorder, but it was hindered by high rates of nonadherence (64%) and dropout (30%) (Crawford MJ et al, *Am J Psychiatry* 2018;175(8):756–764).

In non-bipolar depression, lamotrigine has had mixed results, but it can be used second-line in treatment-resistant depression (TRD). A meta-analysis of eight randomized controlled trials in TRD found a significant effect in patients with longer and more severe episodes (Goh KK et al, *J Psychopharmacol* 2019;33(6):700–713).

Rashes

Lamotrigine's only serious risk is Stevens-Johnson syndrome, which can be fatal if left untreated. Slow titration reduces this risk from 1 in 100 to about 1 in 2,500, but it does not lower the risk of benign rashes, which is quite high at 10% (Bloom R et al, *An Bras Dermatol* 2017;92(1):139–141). Signs of a serious rash include:

- Painful, scaling, or blistering bumps
- Involvement of the face, palms, feet, or mucous membranes
- Systemic signs like fever, lymphadenopathy, malaise, pharyngitis, or muscle aches
- Eosinophilia or elevated liver enzymes

However, there's no reliable way to predict which rashes will progress to Stevens-Johnson syndrome. The FDA labeling recommends stopping lamotrigine at the appearance of any rash or fever in the first 2 months, and it's best to stick with that guidance unless a dermatologist recommends otherwise. Rashes with any of the serious signs above require immediate medical attention and are usually treated with a prednisone taper. To minimize false alarms, advise patients to avoid new soaps and cosmetics, and caution them to avoid sunburn and contact with poisonous plants. Rashes can also appear if lamotrigine is stopped and then restarted after more than 5–7 days, so it's best to retitrate when treatment is interrupted.

What if the patient improves on lamotrigine but a mild rash forces discontinuation? Retitration is feasible, but you'd need to wait at least a month for the inflammation to settle and reintroduce lamotrigine at an extremely slow rate (start 5 mg/day with the chewable 5 mg tablets and raise the daily dose by 5 mg every 2 weeks until reaching 25 mg/day, then follow standard titration).

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This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

How to Use Lamotrigine

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Several case series have tested that strategy in 97 patients. There were no reports of Stevens-Johnson syndrome, but 15% of the retitrations had to be stopped due to new rashes (Aiken CB and Orr C, *Psychiatry* 2010;7(5):27–32).

Other side effects

Outside of allergic rashes, lamotrigine is well tolerated and has no serious medical risks. Here are the most common side effects along with measures to mitigate them (Ramey P et al, *Epilepsy Res* 2014;108(9):1637–1641; Sajatovic M et al, *Patient Prefer Adherence* 2013;7:411–417):

- Nausea, dizziness, and imbalance: Switch to the XR formulation
- Bitter taste: Switch to the orally disintegrating tablets (ODT)
- Word-finding difficulties: Lower the dose
- Insomnia: Switch to morning dosing

Like antipsychotics and tricyclics, lamotrigine can cause photosensitivity, so sunscreen with an SPF above 30 is a good idea.

Folic acid controversy

A patient once called me after adding folic acid to his lamotrigine, complaining that "I feel as bad as I did before I ever started lamotrigine!" Although folic acid has been found to augment valproic acid and antidepressants, in the case of lamotrigine it may nullify the benefits. That was the surprise finding of a large trial in bipolar depression that randomized patients on lamotrigine to adjunctive folic acid 0.5 mg/day or placebo. The mechanism is obscure but seems limited to a subset of patients with the MET variation at the COMT gene, and does not appear to occur with the CNS-active form of folate, l-methylfolate (Tunbridge EM et al, *Bipolar Disord* 2017;19(6):477–486). Until we know more about this interaction, I recommend that patients avoid folic acid while on lamotrigine.

Serum levels

Serum lamotrigine levels are generally not useful in psychiatry. However, you might consider it if the patient has an unusual response and you have reason to suspect their level is off (eg, drug interactions or genetic variations at the UGT1A4 or UGT2B7 enzymes where lamotrigine is metabolized). At doses of 100–250 mg/day, serum levels tend to fall in the 2–6 mcg/mL range (Kikkawa A et al, *Biol Pharm Bull* 2017;40(4):413–418; Douglas-Hall P et al, *Ther Adv Psychopharmacol* 2017;7(1):17–24).

TCPR VERDICT: Bipolar disorder requires long-term prevention, and lamotrigine's tolerability makes it a good choice for this setting. Consider it as monotherapy in bipolar II or as augmentation in bipolar I. Though it can treat acute bipolar depression, it takes about twice as long to work as the atypical antipsychotics.

To learn more, listen to our 1/4/21 podcast, "Mania: The Patient Experience," and our 1/25/21 podcast, "The Birth of Lamotrigine." Search for "Carlat" on your podcast store.

Lamotrigine Dosing

Titration	Adults: Weeks 1–2: 25 mg/day; Weeks 3–4: 50 mg/day; Week 5: 100 mg/day. Children under 16 (based on epilepsy guidelines): Weeks 1–2: 0.3 mg/kg/day; Weeks 3–4: 0.6 mg/kg/day; Weeks 5 and onward: Increase the daily dose by 0.6 mg/kg every 1–2 weeks (always round down to the nearest whole tablet). On valproate: Reduce the lamotrigine dose by 50% at each stage of titration. On carbamazepine, phenobarbital, phenytoin, or primidone: Double the lamotrigine dose at each stage of titration.
Target dose	Adults: 100–250 mg/day. Geriatrics: 50–150 mg/day. Third trimester of pregnancy: 150–400 mg/day. Children under 12 (not FDA approved): 50–150 mg/day. Non-Caucasians may need 25% lower dose due to reduced clearance.
Interactions	Carbamazepine, phenytoin, phenobarbital, primidone, rifampin, and estrogen-containing OCPs lower lamotrigine 40%–50%. Oxcarbazepine at > 1200 mg/day and protease inhibitors lower lamotrigine 30%–50%. Valproic acid raises lamotrigine more than 2-fold. Lamotrigine may lower quetiapine levels 30%. Folic acid may cancel out lamotrigine's benefits (but other forms of folate do not).
Cost	$7/month. XR and ODT are generic but more expensive ($50–$100/month).

Expert Interview

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nerve is cut in a mouse (Bravo JA et al, *Proc Natl Acad Sci* 2011;108(38):16050–16055). Microbes also produce molecules that are important to brain function. Tryptophan, a building block of serotonin, is synthesized by *Bifidobacteria*. Some species produce short-chain fatty acids that we cannot make on our own. Cytokine modulation is another possible route for this brain-gut communication. Cytokines are involved in inflammatory signaling, which has been linked to depression.

TCPR: What's an example of how the microbiota influences behavior?

Dr. Dinan: Well, people with depression have a very different microbiota; it's much less diverse than healthy controls. In our lab we transplanted the microbiota of depressed patients into rodents, and the rodents started to act "depressed." This was a blinded study, and we didn't see any changes in a control group where the transplant came from healthy subjects. And along with that depressive behavior, we saw changes in tryptophan metabolism and elevations of C-reactive protein, a marker of inflammation (Kelly JR et al, *J Psychiatr Res* 2016;82:109–118).

TCPR: Are other psychiatric disorders associated with altered microbiota?

Dr. Dinan: Depression is the most extensively studied. Researchers have also found alterations of

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the gut microbiota in schizophrenia, bipolar disorder, obsessive-compulsive disorder, and autism, but this research is not as robust, and it's not clear whether the alterations are due to differences in eating or other behaviors or whether they are actually playing a causative role in the illness. Recently researchers have found alterations in addictions, and there's a new study where they transplanted microbiota from healthy subjects into patients with alcoholism and found that alcohol cravings were reduced significantly in 90% of the transplant subjects compared with 30% of the placebo subjects (Bajaj JS et al, *Hepatology* 2020; doi:10.1002/hep.31496. Epub ahead of print).

TCPR: Does the microbiota influence social behavior?

Dr. Dinan: It appears to. When mice are raised in a germ-free environment—so they have no microbiota—they are much less likely to interact with other mice. They also have abnormalities in serotonin transmission. We are about to publish a study showing microbiota alterations in social anxiety disorder.

TCPR: How does a person develop a poor microbiome?

Dr. Dinan: Our microbiotas initially develop at birth. If we come into this world through vaginal birth, our initial microbiota is largely determined by the *Lactobacilli* from the birth canal. With Cesarean section, the initial microbiota is radically different and is acquired from microbes on the skin of the doctor, the skin of the mother, and just from the general environment. This is relevant because C-section rates are increasing dramatically around the globe. After that, diet is the main determinant. A fast food diet is not going to produce a healthy microbiota. Medication is another big determinant, and it's not just antibiotics. At least 75% of all the drugs that doctors prescribe impact the gut microbiota, and that figure is even higher for psychiatric medications. Aging is also relevant. The microbiota tends to become less diverse as we age, and frailty follows very rapidly from that.

> **"People with depression have a very different gut microbiota; it's much less diverse than healthy controls. At least 75% of all the drugs that doctors prescribe impact the gut microbiota, and that figure is even higher for psychiatric medications."**
>
> Ted Dinan, MD, PhD

TCPR: On that note, do antibiotics raise the risk of depression?

Dr. Dinan: If you look at meta-analyses of antibiotics, overall they tend to be associated with an increase in rates of depression. The problem with these studies is that infection increases the rate of depression and is potentially a confounding variable.

TCPR: What is the evidence that we can improve mental health by improving the gut microbiome?

Dr. Dinan: First, one of the limitations of this research is that it is relatively new and most of the studies are small (less than a hundred subjects). But there are several dozen placebo-controlled trials now, and here's what they've found. Certain probiotics can reduce stress responses and may improve anxiety and depression. These studies were conducted in patients with major depressive disorder, patients with medical illnesses and comorbid depressive symptoms, and healthy subjects under stress. There is also a large placebo-controlled study where researchers started *Lactobacillus rhamnosus* in the second trimester of pregnancy and it lowered the rate of postpartum depression and anxiety with a large effect size (1.0–1.2); this was a secondary analysis, since they'd set out to look at eczema (Slykerman RF et al, *EBioMedicine* 2017;24:159–165). There are negative studies out there too—our group has published some of them—but on balance the studies in depression, anxiety, and stress lean positive. Most of them used probiotics, but some used prebiotics, live-culture yogurt, or fermented foods.

TCPR: What about other psychiatric disorders?

Dr. Dinan: The results are less consistent in other disorders. There are small studies in schizophrenia, bipolar disorder, and autism. Sleep is an area of growing interest. The microbiota has its own circadian rhythm, and sleep disorders are associated with poor microbiome health. We did a placebo-controlled study showing improvements in sleep with probiotics in university students, and a recent meta-analysis of 14 controlled studies found improvements in sleep quality with probiotics (Irwin C et al, *Eur J Clin Nutr* 2020;74(11):1536–1549).

TCPR: How can people improve their microbiota health?

Dr. Dinan: Diet is the most important way, and aerobic exercise also has a very positive benefit on the microbiota. The Mediterranean and Japanese-style diets are the best studied. I recommend that patients eat more fish, fruit, vegetables, whole grains, and fermented foods; limit red meat consumption to once a week; and reduce processed, fried, sugary, and fast foods. Fruits and vegetable contain over 1,000 identified polyphenols, like resveratrol from grapes and red wine and anthocyanidins from berries, and many of these polyphenols have profound effects both on the gut microbiota and the brain. (*Ed note: See "How to Improve Microbiome Health" table on page 5.*)

TCPR: You mentioned prebiotics. How are these different from probiotics?

Dr. Dinan: Prebiotics are fibers that promote the growth of good bacteria. The most widely studied prebiotic is inulin, which is found in a variety of vegetables: Jerusalem artichoke, onions, celery, and garlic. We also see modulations in the stress response—through reductions of morning cortisol levels—with prebiotics.

TCPR: And probiotics?

Dr. Dinan: Probiotics are the bacteria themselves, which we can take in capsule form. The FDA actually prefers the word "live biotherapeutics" because so many supplement companies have made outrageous health claims about probiotics. But in terms of educating our patients, we know that *Lactobacilli* and *Bifidobacteria* are good for us. But I'm a big

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believer that the best source of most nutrients is in good food—not in a capsule. So eating yogurt with live cultures, drinking kefir and kombucha, consuming kimchi and other fermented foods—these are all extremely good sources of probiotic bacteria.

TCPR: Why do you prefer dietary change over probiotic capsules?

Dr. Dinan: A healthy diet does so much more than just change the microbiome. It's important for vascular and metabolic health, and it has many effects on the brain. There's polyphenols that offer neuroprotection; omega-3s that are the building blocks of neural cell membranes; and folate and other vitamins that are involved in neuropeptide production. Food is also the ideal delivery system, but if the patient can't change their diet, then a capsule is the next best thing.

TCPR: Are there any risks with probiotics?

Dr. Dinan: You should avoid probiotics in people who are dramatically immunocompromised. Outside of that, I don't see much of a risk as long as the product was appropriately produced. The only risk is that it may have no impact whatsoever.

TCPR: How would you guide a patient to choose a probiotic?

Dr. Dinan: *Bifidobacteria* and *Lactobacilli* are the most widely studied genuses of bacteria for their anti-anxiety and anti-stress effects. I'd also look for a probiotic from a reputable company. Generally, the bigger companies are more likely to produce a high-quality product and not make outlandish claims that would attract the ire of the Food and Drug Administration (FDA) or the European Food Safety Authority (EFSA).

How to Improve Microbiome Health

Dietary Prebiotics	
These foods provide nutrient support to maintain a healthy microbiome. Use them as part of a healthy, Mediterranean-style diet that is low in red meat, fast food, processed foods, and sugary and fried foods.	
Inulin and fructooligosaccharides	Onion, garlic, leeks, asparagus, bananas, artichoke, dandelion greens, chicory, blue agave, jicama root, yacon root, wheat bran
Polyphenols	Fruits and berries, vegetables, walnuts, wine, tea, coffee, dark chocolate, turmeric
Polyunsaturated fatty acids	Oily fish, flax seeds, walnuts, oils (canola, corn, soybean, safflower)
Other	Barley, oats, seaweed
Dietary Probiotics	
These foods contain live probiotics.	
Dairy	Yogurt, kefir, cottage cheese (look for products with live cultures), aged cheeses (cheddar, mozzarella, gouda, parmesan, and swiss)
Fermented foods	Pickles brined in salt water (not vinegar), olives, sauerkraut, tempeh, kimchi, miso, natto, poi
Drinks	Kefir, kombucha, non-alcoholic ginger beer, shrubs (vinegar drinks), Indian lassi, Russian beet kvass, apple cider vinegar
Probiotic Capsules	
These can supplement a healthy diet. The products below were approved by ConsumerLabs or US Pharmacopeia and contain strands with mental health benefits.	
Low cost ($0.20/day)	TruNature Advanced Digestive Probiotic (Costco), Member's Mark 10 Strain Probiotic (Sam's Club)
Higher cost ($0.60–$1.20/day)	Bayer Phillips Colon Health, Dr. Mercola Complete Probiotics, Garden of Life Raw Probiotics Ultimate Care or Once Daily Women's, GNC Probiotic Complex, Jamieson Probiotic 5 Billion, Nature's Way Fortify Daily 30 Billion, PB8, Pure Encapsulations Probiotic GI, Visbiome High Potency Probiotic, Hyperbiotics PRO-Women
Lifestyle	
Exercise	Microbiota diversity improves with aerobic exercise
Sleep	Insomnia, poor sleep quality, and jet lag are associated with poor microbiome health
Stress reduction	Both active and early-life stress impair microbiota health, and poor microbiome health worsens stress-related disorders

TCPR: Which is better: a probiotic with a single strand of bacteria, or a combination of strands?

Dr. Dinan: We don't have definitive studies on that, but a recent meta-analysis suggests that multiple probiotics—which we call polybiotics—are more effective than single strains in depression (Goh KK et al, *Psychiatry Res* 2019;282:112568).

TCPR: Do probiotics need to be refrigerated?

Dr. Dinan: Not necessarily. The bacteria in capsules are freeze dried—they are in a dormant state—so refrigeration probably doesn't make a big difference as long as the capsules aren't stored at an exceedingly high temperature. Bacteria are incredibly resilient. One thing that can kill them off, though, is acid, and some of these probiotics won't make it through the acidity of the stomach.

TCPR: Researchers are also changing the microbiota through fecal transplant. Do you think we'll ever see that approach used in clinical practice?

Dr. Dinan: Right now the only indication for fecal transplant is treating chronic *C. difficile* infection in elderly people. They have been used experimentally in psychiatry, for example in autism and alcoholism, but the procedure has risks—you could be transmitting a virus that wasn't picked up in the original donor sample. My hope is that one day we'll develop artificial feces that might have eight or nine probiotics in it. We just need to find out the key microbes for optimal health and artificially grow them.

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

To learn more, listen to our 1/18/21 podcast, "Probiotics and Depression: An Interview With Ted Dinan." Search for "Carlat" on your podcast store.

Research Updates IN PSYCHIATRY

BENZOS

Rest Easy: Benzos, Z-Drugs, and Dementia

REVIEW OF: Osler M and Jorgensen MB, *Am J Psych* 2020;177(6):497–505

STUDY TYPE: Epidemiologic case-control

Few psychotropics stir controversy like the benzodiazepines. While they work well for anxiety and insomnia, their risks of abuse and dependence have always nagged at us. More recently, some research has suggested that long-term use increases the risk of dementia. Those studies did not control for subjects' underlying diagnoses, and this new study partially overcomes that problem by focusing on a homogenous diagnostic group.

This cohort and nested case-control study drew its data from Danish hospital and pharmacy registries. The cohort of roughly 235,000 subjects was comprised of patients who presented for their first hospitalization for a mood disorder. These patients were assessed for dementia at that first visit and followed for 3–11 years. The primary outcome was the difference in the rate of dementia between those who were started on a benzodiazepine or z-hypnotic and those who were not.

Dementia can present with symptoms of depression, so it's possible that some of the patients who converted to dementia were in the early phase of cognitive decline at the start of the study. To control for that, patients who converted to dementia in the first two years were analyzed separately.

The researchers adjusted for a number of variables including gender, age, marital status, education, depression subtype, year of diagnosis, psychotropic medication use, and comorbidity. The thoroughness of their adjustments and generalizability are what make this study stand apart from prior, similar case-control and prospective studies. The data collected from the registries allowed the researchers to see all diagnoses, prescribed medications, amounts of medications filled, hospitalizations, timing of diagnoses, and even data prior to study entry.

In their analysis, the authors found that out of the study cohort, 4% were diagnosed with dementia. Unexpectedly, there was a decreased risk of dementia in the first 2 years after study entry if a benzodiazepine or z-drug was prescribed (hazard ratio 0.70; range 0.66–0.74). For years 2 through 20 after study entry, there was no association between dementia and use of benzodiazepines or z-drugs, even when stratifying based on number of prescriptions, duration of use, combined use, and half-life.

TCPR'S TAKE

While it does not completely close the door on the controversy, this study significantly weakens the links between benzos, z-hypnotics, and dementia. However, these medications do have other cognitive side effects separate from any dementia risk, and their use still warrants caution in the elderly due to their risks of falls, traffic accidents, and respiratory suppression. Low doses of short-acting benzodiazepines like lorazepam and oxazepam minimize those risks.

—James Jenkins, MD. Dr. Jenkins has disclosed that he has stock in Alkermes, Sage Therapeutics, Teva Pharmaceutical Industries, Trevena, and Viatris. Dr. Aiken has reviewed this article and has found no evidence of bias pertaining to this educational activity.

DEPRESSION

Beta Blockers and Depression: The Controversy Revisited

REVIEW OF: Agustini B et al, *J Hum Hypertens* 2020;34(11):787–794

STUDY TYPE: Cross-sectional

Antihypertensives are among the world's most widely prescribed drugs, but many of them impact pathways associated with depression. Beta blockers have long been believed to cause depression, but most of the studies suggesting this were carried out decades ago and their findings have been inconsistent. Other classes, like angiotensin-receptor blockers, are associated with lower rates of depression, albeit with weaker evidence.

In this multinational study, researchers examined mood outcomes in 14,195 hypertensive adults over age 65 who did not have heart disease. Depressive symptoms were measured with the self-reported Centre for Epidemiological Studies-Depression (CESD-10) scale. Each class of antihypertensive drugs was tested against the other classes and against a group of unmedicated hypertensive patients to see whether any class was associated with an increased risk of clinically significant depressive symptoms.

Patients who took beta blockers were more likely to meet or exceed the clinical cutoff score of 8 on the CESD-10 scale, a sign of clinically significant depressive symptoms, than those who took other antihypertensive drugs. Numerically, 13.4% of patients who used beta blockers showed clinical elevations in depression, whereas between 10.2% and 10.5% of patients who used other antihypertensives showed this elevation. Logistic regression analysis showed that this difference was indeed significant, even when controlling for numerous factors that included gender, age, and smoking history. Other classes of antihypertensives, including angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, and calcium-channel blockers, were not associated with depression.

The researchers also compared the beta blockers based on their selectivity for the β-receptor and their lipophilic properties. Lipophilic medications are more likely to cross the blood-brain barrier, and the more lipophilic beta blockers like propranolol and metoprolol were associated with a higher

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CME Post-Test

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

1. Stevens-Johnson syndrome, a potentially fatal rash associated with lamotrigine use, occurs in about 1 in 2,500 patients. What is the risk of benign rashes on lamotrigine? (LO #1)

   [ ] a. 1% [ ] b. 5% [ ] c. 10% [ ] d. 15%

2. A 2020 study showed what association between dementia and patients who were prescribed a benzodiazepine or z-drug in the first 2 years after study entry and for subsequent years 2 through 20? (LO #3)

   [ ] a. Increased risk of dementia for both years 0–2 and years 2–20
   [ ] b. Increased risk of dementia for years 0–2; no association in years 2–20
   [ ] c. No association with risk of dementia for years 0–2; increased risk in years 2–20
   [ ] d. Decreased risk of dementia for years 0–2; no association in years 2–20

3. According to Dr. Dinan, which of the following is associated with poor microbiome health? (LO #2)

   [ ] a. Low birth weight
   [ ] b. Family history of bipolar disorder
   [ ] c. Poor sleep quality
   [ ] d. Indoor living

4. Lamotrigine is FDA approved for bipolar disorder and has also been useful as an off-label treatment for which condition? (LO #1)

   [ ] a. Panic disorder
   [ ] b. Impulse control disorders
   [ ] c. Obsessive-compulsive disorder
   [ ] d. Alcohol use disorders

5. A 2020 study showed no relationship between patients taking either antihypertensives or beta blockers and the onset of depression. (LO #3)

   [ ] a. True [ ] b. False

Research Updates

Continued from page 6

risk of depression than hydrophilic ones like atenolol. Meanwhile, the more selective beta blockers were less depressogenic, which weakens the argument that blockade at this receptor plays a causative role in depression.

TCPR'S TAKE

The fact that beta blockers were associated with depression while other antihypertensives were not gives us pause, but the risk here is very small (3%). If beta blockers must be used in depressed patients with hypertension, stick with atenolol. Whether this risk translates to the psychiatric use of propranolol—which generally involves lower doses and normotensive patients—remains unanswered.

—Sean Ransom, Ph.D

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

In Brief: The Queen's Gambit

A seven-hour series about chess tournaments doesn't sound like a blockbuster, but *The Queen's Gambit* is currently the #1 show on Netflix. The show makes a bold opening move by casting a woman in the role of the young champion—an unlikely choice, but one that stands on strong empiric ground.

Only 1% of chess grandmasters are women, but this gender gap appears to be caused by a lack of participation rather than a lack of talent. A study of 250,000 players found that male and female players had comparable abilities when they entered tournament play. Girls were more likely to leave the competitive circuit early, but the ones who stayed with it advanced at the same rate as boys (Chabris CF and Glickman ME, *Psychol Sci* 2006;17(12):1040–1046).

A separate study arrived at the same conclusion by applying a statistical model to the top 100 players. At this level, the men had higher scores on average, but 96% of the difference was attributable to the vast discrepancies in participation between men and women (BilaliĆ M et al, *Proc Biol Sci* 2009;276:1161–1165).

The Queen's Gambit wins the game with gender, but the show blunders when it comes to psychopharmacology. The protagonist uses barbiturates throughout the series to enhance her game. In reality, these amnestic and sedative agents would have the opposite effect. Looking at the bigger picture, however, the point unfortunately stands: 1 in 10 tournament chess players admit to using cognitive enhancers to improve their game.

To learn more, listen to our 1/11/21 podcast, "Chess and Psychiatry in The Queen's Gambit." *Search for "Carlat" on your podcast store.*

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Mind-Gut Connection
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Next Issue:
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Carlat Publishing News

Updates on additional clinical resources we're working on

Newsletters:

The Carlat Child Treatment Report: The year-end 2020 issue covers mood disorders in children and adolescents, while the Jan/Feb/March 2021 issue will tackle cultural-related topics.

The Carlat Addiction Treatment Report: The current Nov/Dec 2020 issue explores alternative therapies in addiction treatment, while the upcoming Jan/Feb 2021 issue covers pain and addiction.

NEW! *The Carlat Hospital Treatment Report:* We're adding a fourth offering to our newsletter list! *The Carlat Hospital Treatment Report* will launch in 2021. Stay tuned for more details about the publication date of its inaugural issue.

Current book titles include:

The Medication Fact Book for Psychiatric Practice (Fifth Edition)
Available with 12 CME credits

NEW! *Practice Boosters (Third Edition)*
Available December 2020 with 12 CME credits

The Child Medication Fact Book for Psychiatric Practice
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