THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today!
Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief

Volume 19, Issue 5
May 2021
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Problems With Generics

A Review of Medications for PTSD, With a Focus on Topiramate — 1

Expert Q&A: — 1
Katherine Eban
What's Wrong With Generics?

Depression, Vitamin D, and COVID-19 — 5

Tables:
- Seven Medications for PTSD — 2
- Generic Stumbles From the Past — 4
- Vitamin D: Quick Facts — 7

Research Update: — 6
- Maintenance Pharmacotherapy of Bipolar Disorder: How Long Is Long Enough?

CME Test — 7

In Brief: Lamotrigine Gets a New Warning — 8

Learning Objectives

After reading these articles, you should be able to:

1. Evaluate the current pharmacological treatments for PTSD.
2. Describe the role of vitamin D in both depression and COVID-19.
3. Identify safety and efficacy challenges specific to generic medications.
4. Summarize some of the current research findings on psychiatric treatment.

A Review of Medications for PTSD, With a Focus on Topiramate

Paul Riordan, MD. Assistant Consulting Professor of Psychiatry, Duke University.

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

Highlights From This Issue

Topiramate is not first-line in PTSD, but it does have a role, particularly when alcohol use is part of the picture.

Katherine Eban explains the rush of recalls on generic medications and the limitations of FDA oversight.

When a patient with bipolar disorder stops their mood stabilizer, the risk of relapse nearly doubles, from 32% to 52%.

A new patient comes into your office for an assessment. He tells you he cannot keep living this way. He shops at Walmart at 3 am to avoid strangers. He startles easily and suffers from nightmares and flashbacks related to a trauma he experienced in the Army. He's tried sertraline and venlafaxine for PTSD but did not find them helpful and wants to try something else. You offer a referral for trauma-focused therapy, but he refuses, saying "I don't want to talk to anyone."

Are there any other medications that could help? When it comes to PTSD, trauma-focused therapy is first-line. It is backed by solid data with a large effect size, while medications have only mild treatment effects (Lee DJ et al, *Depress Anxiety* 2016;33(9):792–806). A possible exception to this rule is that patients who choose their preferred treatment do

Continued on page 2

Q&A With the Expert

What's Wrong With Generics? Katherine Eban

Katherine Eban is an investigative journalist whose 2019 book Bottle of Lies: The Inside Story of the Generic Drug Boom *uncovered problems in generic drug manufacturing.*

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

TCPR: What's wrong with generic drugs?

Ms. Eban: That's the question that got me started. In 2008, I got a phone call from Joe Graedon, the pharmacologist who hosts the NPR program *The People's Pharmacy.* He was getting complaints from listeners who were saying that their generic drugs were either causing troubling side effects or weren't effective anymore. So I started investigating, and it led me on a decade-long inquiry, ending up in India and China where the majority of our low-cost drugs are made.

TCPR: What did you find?

Ms. Eban: I began looking into the conditions in those manufacturing plants, and it's really like something out of Upton Sinclair's *The Jungle:* just a very troubling web of fraudulent data, substandard conditions, and manufacturing plants with snakes and monkeys and bird droppings. In one case a company

Continued on page 3

A Review of Medications for PTSD, With a Focus on Topiramate

Continued from page 1

better when they receive their choice—meaning patients who prefer pills do better when they get pills (Mergl R et al, *Psychother Psychosom* 2011;80(1):39–47).

Which medications work in PTSD?

Sertraline and paroxetine have FDA approval in PTSD, but there is nothing about the pathophysiology of PTSD that points to SSRIs as the cure. In some countries, SSRIs did not gain approval because they mainly worked in civilian trauma and not military trauma, but military trauma is more difficult to treat whether with medications or therapy. A new meta-analysis—the largest to date—compared effect sizes of 26 medications across 58 studies that had a total of nearly 7,000 patients with PTSD (de Moraes Costa G et al, *J Psychiatr Res* 2020;130:412–420).

What did the study find? Only seven medications—fluoxetine, paroxetine, quetiapine, risperidone, sertraline, topiramate, and venlafaxine—were better than placebo (see table below). Missing from this list is prazosin; it no longer passes statistical muster due to a large negative trial of 304 veterans with PTSD (Raskind MA et al, *N Engl J Med* 2018;378(6):507–517), but there were flaws with that study that lead some to believe prazosin does work in a subset of patients (see *TCPR,* April 2019).

As expected, the SSRIs and SNRIs had small benefits, with effect sizes ranging from 0.2 to 0.35—about the same as the small effect sizes observed for antidepressants in depression (Ormel J et al, *Psychol Med* 2019;50(2):177–186). Fluoxetine had the best balance of efficacy and acceptability, but that was mainly due to high tolerability, since its benefit was small. Despite the small effect sizes, our confidence in those benefits is high, with each medication having 650–1,400 total participants across their trials.

In contrast, the effect sizes were larger (0.5–0.6) for a few off-label medications: topiramate, risperidone, and quetiapine. However, there were only a few studies backing these medications, with only 70–100 patients each—so while they show promise, it's not definite since small studies are notorious for inflated effect sizes.

Benefits of topiramate for PTSD

Most surprisingly, topiramate came out on top as having the greatest benefit for PTSD, with a medium effect size (0.57). There is a lot of uncertainty around that figure, as it was based on only two randomized trials involving 73 civilian patients. However, three randomized trials of 137 veterans were excluded because they focused on treatment-resistant PTSD (two studies) or on comorbid alcohol use disorder with PTSD symptoms as a secondary outcome (one study). If these studies are included, the total n becomes 210, with one positive

Continued on page 3

Seven Medications for PTSD

Medication	FDA Approved?	Daily Dose	Advantages	Disadvantages
Fluoxetine	No	20–60 mg	Best tolerated in PTSD; low risk of serotonergic withdrawal problems	Drug interactions
Paroxetine	Yes	20 mg	FDA approval	Withdrawal problems and anticholinergic side effects
Quetiapine	No	100–300 mg	Improves nightmares, sleep quality, and comorbid disorders (bipolar, depression, GAD)	Side effects (fatigue, orthostasis, metabolic, anticholinergic, TD); limited evidence supporting use in PTSD
Risperidone	No	2–3 mg	Improves comorbid disorders (bipolar mania, psychosis, and possibly antidepressant augmentation)	Side effects (EPS, metabolic, TD); limited evidence supporting use in PTSD
Sertraline	Yes	75–200 mg	Good safety profile in the medically ill	Slow titration may be needed to avoid GI distress
Topiramate	No	100–300 mg	Useful for comorbid alcohol use disorder and migraines; improves sleep and nightmares	Limited evidence supporting use in PTSD
Venlafaxine	No	75–300 mg	Also helps panic disorder at doses of 225–300 mg/day	Withdrawal problems, hypertension

A Review of Medications for PTSD, With a Focus on Topiramate

Continued from page 2

trial, three trials trending toward significance, and one negative trial. The negative trial, which focused on treatment-resistant PTSD in veterans, had a high dropout rate due to side effects (Lindley SE et al, *J Clin Psychopharmacol* 2007;27(6):677–681). In the other trials, while topiramate caused side effects like dizziness, paresthesias, and memory problems, it did not lead to more dropouts.

What did topiramate help with? Across studies, it appeared most helpful for the "reexperiencing" symptoms—flashbacks, intrusive memories, and nightmares, with less benefit for avoidance and numbing symptoms.

Topiramate demonstrated other benefits relevant to PTSD. For example, in one trial, veterans with PTSD who took topiramate had 55% fewer standard drinks per week than those taking placebo (Batki SL et al, *Alcohol Clin Exp Res* 2014;38(8):2169–2177). Topiramate is also FDA approved for migraine prophylaxis and—based on small controlled trials—may help with obesity, borderline personality disorder, cocaine abuse, and impulse control disorders (Nourredine M et al, *CNS Drugs* 2021;35(2):177–213; Varghese BS et al, *Indian J Pharmacol* 2010;42(3):135–141). Unlike the antidepressants, it is safe in bipolar disorder.

How to use

Slow titration is recommended for topiramate's FDA-approved indications (migraines and epilepsy), and we have found that strategy helpful in reducing side effects like dizziness and cognitive impairment. For PTSD, start at 25 mg nightly and raise by no more than 25 mg/week toward a target dose of 100–300 mg daily. With a 21-hour half-life, nightly dosing is acceptable, but opt for divided dosing if the patient experiences side effects as the level peaks.

The most common side effects to watch for are dizziness, paresthesias, somnolence, and cognitive impairment. For cognition, topiramate typically affects word finding and verbal fluency—tested by listing as many animals as possible in 60 seconds (Thompson PJ et al, *J Neurol Neurosurg Psychiatry* 2000;69(5):636–641). Rare side effects to watch for include kidney stones, glaucoma, increased body temperature, and metabolic acidosis.

TCPR VERDICT: Topiramate has potential as second- or third-line pharmacology for PTSD after a trial of SSRIs/SNRIs, and it may be closer to first-line for patients with comorbid alcohol use disorder.

To learn more, listen to our 5/17/21 podcast, "13 Ways to Use Topiramate." Search for "Carlat" on your podcast store.

❖ ❖ ❖

Expert Interview

Continued from page 1

was steaming fabricated documents overnight in a sauna-like room to make them look old.

TCPR: How does this kind of thing get past inspectors?

Ms. Eban: At US plants, the FDA conducts surprise inspections, but with overseas plants they announce their inspections in advance, so these plants have months to launder their true conditions. Essentially, they create a stage set of compliance that does not reflect what is actually going on in the plants. That is what I was able to uncover by obtaining documents, speaking with investigators, and talking to whistleblowers.

TCPR: Your book talks about antibiotics that don't reach therapeutic levels, dangerous contaminants, and—closer to home for psychiatry—extended-release (ER) mechanisms that break down, like generic Wellbutrin XL. What happened there?

Ms. Eban: That was one of the medications that Joe Graedon was hearing a lot of complaints about from his listeners. First he wrote the FDA about it but they took no action. Then he got ConsumerLab to test Teva's generic Wellbutrin XL, and lo and behold, the generic dumped the active ingredient into the bloodstream much faster than the brand. It was like guzzling three glasses of wine as opposed to drinking them over the course of a day. The patients were complaining of dizziness, suicidal thoughts, and nausea. That discovery shamed the FDA into conducting their own study, and that generic was forced from the market. Then one of the FDA officials who had spent years telling Joe Graedon "everything was fine" ended up going to work at Teva, which was essentially the company the official had been protecting for years.

TCPR: Why do we see more problems with ER medications? Can't a company just make an identical ER mechanism after the patent runs out?

Ms. Eban: The mechanisms may be in the public domain, but the manufacturing techniques are not. The brand-name companies don't turn over their recipes, so everything has to be reverse-engineered.

TCPR: When did generic manufacturing start to move overseas?

Ms. Eban: It started slowly in the 1980s and quickened with the launch of the new century. By 2004 the FDA had more overseas plants to inspect than it did within the US.

TCPR: Have the brand-name manufacturers also shifted overseas, or is this just affecting generics?

Ms. Eban: Western brand-name companies have bought up a number of manufacturing plants overseas, so this is not a problem that is exclusive to generics. In the book, I do feature a number of brand-name companies who are essentially getting duped within their own plants by supervisors who are faking data. But the bigger problem is driven by the financial model of the generic drug industry. Profit margins are slim, because generic competition causes the prices to plunge. That leaves little incentive for quality.

TCPR: How widespread is this problem?

Ms. Eban: There aren't a lot of data on this, but here's a metric. The book features a young FDA

Continued on page 4

Expert Interview
Continued from page 3

investigator named Peter Baker. He inspected 86 plants in India and China over four years, from 2012 to 2016, and found evidence of fraud in four-fifths of those plants. So it's fairly widespread.

TCPR: How did he uncover the fraud?

Ms. Eban: Instead of relying on data printouts, Baker looked into the plants' computer systems, and there he found metadata evidence of test manipulation. Some plants were secretly pretesting their drugs to see if they would pass, and if they wouldn't then they'd manipulate the testing parameters. They'd delete those pretests, which they were supposed to share with the FDA.

TCPR: Your book focuses on India and China. Have you seen this problem in other countries?

Ms. Eban: I don't think it's unique to those countries, but regulatory breakdowns have made it more common there. The plants in India and China are not being scrutinized by their own regulators, so the scrutiny is left up to the FDA, and thus it's become a game of how to trick the FDA inspectors.

TCPR: Did your investigations uncover any hope?

Ms. Eban: The book tells the story of a heroic whistleblower who exposed incredible wrongdoing in India's largest drug company, and he did so at incredible risk to himself and his family. That's basic hope in humanity.

TCPR: What happened to the drug company he exposed?

Ms. Eban: That company was Ranbaxy. They no longer exist, but before 2014 they manufactured several dozen generics, including gabapentin, nefazodone, atorvastatin, and pantoprazole. Although the company was eventually brought down by the investigations, the conditions that gave rise to the fraud inside Ranbaxy have not necessarily changed. There are more Ranbaxys. I think we need to realize that we can't really separate the issue of cost from quality. We need to build a system that incentivizes quality in generics, and I see some evidence of that happening.

TCPR: Seems like a simple change would be for the FDA to conduct surprise visits overseas.

Ms. Eban: The FDA had been relying on overseas companies to organize their travel. After the book came out, there were some congressional hearings where the FDA announced that they would stop that practice, but this is not a wholesale change in how they operate—their visits are still announced. COVID-19 has further derailed attempts at improvement because the FDA has put overseas inspections on hold during the pandemic. On the other hand, COVID-19 has accelerated our understanding of the grave risks of being dependent on foreign countries for lifesaving supplies. There is a movement in the US to reshore our pharmaceutical supply chain.

TCPR: We've seen a lot of drug recalls lately, like metformin ER. Are these just honest mistakes, or are they indicative of the larger problem?

Ms. Eban: These recalls are part of the problem. There is basically a worldwide scandal in which a carcinogen called NDMA was found in metformin ER, ranitidine, and several of the "-sartan" angiotensin II receptor blockers. An FDA inspector had actually identified problems in a plant in China where they were not investigating impurity spikes in their own drugs. He flagged that, but his supervisors at the FDA ignored the finding. The FDA has become increasingly industry-friendly and often downgrades the findings of its own inspectors.

TCPR: You've uncovered clear problems. Are doctors seeing the results?

Continued on page 6

Generic Stumbles From the Past	
Anticonvulsants	Anticonvulsants have a narrower therapeutic window in epilepsy than bipolar disorder. Hence, there are reports of increased seizures after switching to generic lamotrigine, carbamazepine, and valproic acid, but this has not clearly translated to problems in bipolar disorder.
Bupropion and Venlafaxine	Some specific extended-release versions of these antidepressants—venlafaxine XR and Budeprion XL (Teva's branded generic bupropion XL)—had a tendency to dump the entire dose shortly after taking it, resulting in side effects in the morning and withdrawal problems in the afternoon. Both were made by Teva. The problematic budeprion XL has since been withdrawn from the market.
Citalopram	There is one report from 2007 of worsened panic disorder in 20 patients who switched from branded Celexa to generic citalopram. The patients were not aware of the switch, and they improved with return to the brand (Van Ameringen M et al, *J Psychopharmacol* 2007;21(5):472–476).
Clozapine	There were reports of increased relapses when patients switched from branded to generic clozapine in 2001, particularly with the Zenith generic (later bought by Teva). A more recent analysis concluded this problem is rare and best managed by measuring the serum levels.
Concerta	Two generics were withdrawn in 2016 for releasing the medication too slowly (made by Mallinckrodt and UCB/Kremers; Actavis was unaffected).
Levothyroxine	You may hear it said that levothyroxine is not bioequivalent to the branded form, Synthroid. This was true in 1980 when a paper was published in *JAMA* exposing the discrepancy. Four years later the same authors reported that the manufacturing problem had been corrected, and in 1997 a study of four levothyroxine products found no difference among them (Dong BJ et al, *JAMA* 1997;277(15):1205–1213). Still, the rumor persists.

"Clinicians usually don't know which generic their patient is taking. But if they have a patient who's suddenly become unstable, it might be worth finding out if the pharmacy dispensed drugs from a different manufacturer."

Katherine Eban

Depression, Vitamin D, and COVID-19

Paul Riordan, MD. Assistant Consulting Professor of Psychiatry, Duke University.

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

Your patient with a history of depression comes to see you with a magazine article in hand. She has read that vitamin D deficiency causes depression and wants to know if she can get hers checked.

Based on what we already know about this patient, there's a good chance her levels are low. In the US, 1 in 4 people have low vitamin D levels, and the rate is even higher among psychiatric patients. Up to 1 in 3 persons with depression and 3 in 5 persons with bipolar disorder or schizophrenia have vitamin D levels < 20 ng/mL (Boerman R et al, *J Clin Psychopharmacol* 2016;36(6):588–592). But is it worth checking? And will supplementation help this patient's mood? In this article we'll review the research on vitamin D and depression, as well as its role in general health and COVID-19.

Vitamin D and psychiatric disorders

First, some basics. Vitamin D's main function is to help us absorb calcium, which is necessary for bone strength. We can maintain our stores of vitamin D in two ways: by taking supplements or exposing ourselves to natural sunlight for at least 15 minutes three times per week. Long-term vitamin D deficiency causes a range of health problems, including low birth weight, rickets, fractures, and possibly even cancer, cardiovascular disease, and death (Theodoratou E et al, *BMJ* 2014;348:g2035). More controversial is whether less extreme deficiencies ("insufficiencies") of vitamin D can cause more subtle problems with energy or mood.

Basic science research from the last two decades has established some biologic plausibility for the role of vitamin D in mental health. For example, rats deprived of vitamin D develop several neurologic deficits that are commonly seen in schizophrenia, such as increased lateral ventricle size. These and other animal studies suggest that vitamin D is important for brain growth and differentiation (Eyles DW et al, *Front Neuroendocrinol* 2013;34(1):47–64). Beyond its role in brain development, vitamin D also modulates stress hormones (Menon V et al, *Indian J Psychol Med* 2020;42(1):11–21).

Epidemiological studies of variable quality show that low levels of vitamin D are associated with the development of autism, schizophrenia, seasonal affective disorder, and depression—although the evidence is very weak for autism and seasonal affective disorder. For schizophrenia, one high-quality case control study with 3,464 participants showed that the risk of developing schizophrenia was 44% higher among neonates with the lowest levels of vitamin D (< 8 ng/mL) compared to those with levels between 16 and 21 ng/mL (Eyles DW et al, *Scientific Reports* 2018;8:1–8).

For depression, one important meta-analysis from 2013 showed participants with the lowest levels of vitamin D had a 30% increased odds of developing depression, although this was not quite statistically significant (OR 1.31 [95% CI: 1.0–1.71] (Anglin RES et al, *Br J Psychiatry* 2013;202:100–107). But since our vitamin D stores are largely made by exposure to sunlight, all of these epidemiologic studies are confounded by the possibility that vitamin D levels may reflect lifestyle choices. In other words, it's possible that people with mental illness are more likely to spend more time indoors—which would cause low vitamin D levels. Low vitamin D may be the result of depression rather than the cause.

But what about treatment? For that, we turn to randomized controlled trials. Nearly all are in depression, and the results are mixed.

First, supplementing vitamin D in healthy persons without depression does not prevent the development or recurrence of depression (Okereke OI et al, *JAMA* 2020;324(5):471–480). Supplementation is also not helpful for depressed individuals who do not have vitamin D insufficiency or deficiency (Menon et al, 2020). It may, however, be helpful as an adjunct treatment for persons with clinical depression and with levels < 20 ng/mL. There are two positive and two negative randomized controlled trials, with various flaws on both sides, from small sample size to lack of blinding (Menon et al, 2020).

Overall, the best we can say is that little harm seemed to occur from supplementation, with only 5 of 362 participants who received high-dose vitamin D stopping the vitamin due to side effects (Wang Y et al, *J Clin Psychopharmacol* 2016;36(3):229–235). For bipolar disorder, the evidence for supplementation is even weaker, with one tiny positive trial (n = 16) and one slightly larger negative trial (n = 33) (Cereda G et al, *J Affect Disord* 2021;278(1):209–217).

Low vitamin D and COVID-19

What conditions remain where vitamin D supplementation may be helpful? While low vitamin D has been linked to multiple health problems, clinical trials of vitamin D supplementation for most of these conditions have also been disappointing (Bolland MJ et al, *Lancet Diabetes Endocrinol* 2018;6(11):847–858).

Many people are supplementing with vitamin D to prevent COVID-19 infection, and there is some logic behind that if their levels are low. There is strong evidence that vitamin D helps prevent respiratory tract infections. A recent meta-analysis suggested a 9% reduction in the likelihood of experiencing at least one acute respiratory infection (Jolliffe DA et al, *medRxiv* 2020 [preprint]; PMID: 33269357).

Current studies on vitamin D and COVID-19 are limited but intriguing. In the only randomized controlled trial on vitamin D supplementation in COVID-19 patients, only 2% of the patients in the vitamin D_3 group required admission to the ICU compared to 50% of the patients in the placebo group (Castillo ME et al, *J Steroid Biochem Mol Biol* 2020;203:105751). That sounds impressive, but the study was small (n = 76) and the randomization imperfect (there were more patients with diabetes—which itself worsens COVID-19 prognosis—in the placebo group).

Continued on page 7

Research Update IN PSYCHIATRY

BIPOLAR

Maintenance Pharmacotherapy of Bipolar Disorder: How Long Is Long Enough?

REVIEW OF: Kishi T et al, *Psychol Med* 2020 Oct 13:1–9; PMID: 33046156

TYPE OF STUDY: Meta-analysis of double-blind, randomized placebo-controlled trials

Bipolar disorder is a lifelong illness whose treatment is an ongoing challenge, complicated not least by difficulties in treatment adherence. What do we know and what can we tell our patients about how long to continue medication?

This meta-analysis looked at recurrence rates of any mood episode in bipolar disorder after 6 months of maintenance treatment vs discontinuation of medication. The authors analyzed 22 double-blind, placebo-controlled studies of second-generation antipsychotics (LAI or oral) or a mood stabilizer in adults with bipolar I or II disorder that included a maintenance phase lasting at least 12 weeks. Some studies recruited stable subjects, while others were extensions of acute treatment studies after initial stabilization. Results were also broken down by relapse into episode subtypes: depressive, manic/hypomanic/mixed, as well as all-cause discontinuation from the study.

Compared to drug discontinuation, maintenance treatment was associated with a lower recurrence rate at 6 months for all mood episodes. The relative risks (RR) for those who remained on medication were 0.61 for any episode, 0.72 for depressive episodes, 0.45 for manic/hypomanic/mixed episodes, and 0.71 for all-cause discontinuation. The raw relapse rates into any mood episode at 6 months were 32.3% with maintenance vs 52.7% with discontinuation. In subgroup analyses, oral second-generation antipsychotics had better preventative properties than lithium or lamotrigine, based on their RRs. However, all but one of the eight SGA studies (nine groups) were "enriched"—that is to say, they included only subjects who had proven to be responsive to medication—while only two of the 15 lithium studies were enriched, making direct comparisons invalid. Oral antipsychotics were superior to long-acting injectables at preventing depression, which is not surprising considering none of the FDA-approved options for bipolar depression (cariprazine, lurasidone, quetiapine, and olanzapine-fluoxetine combination) are available in injectable form.

One limitation is the possibility that some of these relapses represented withdrawal phenomena, as most studies discontinued the medication abruptly. Also, the majority of relapses occurred at the very beginning of the follow-up period, which raises the possibility that withdrawal effects contributed to the relapse risk.

TCPR'S TAKE

Long-term maintenance medication is the norm in bipolar disorder, and this study backs up that standard. When patients want to stop their primary mood stabilizer, we can advise them that they are twice as likely to stay well if they stick with it. It may be feasible to come off an augmentation agent, however, if they have been well for at least 6 months and keep the primary mood stabilizer on board (see *TCPR* Jan 2020 on antipsychotic maintenance). Slow discontinuation (eg, over 1–6 months) also reduces the relapse risk, particularly with lithium.

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

To learn more, listen to our 5/31/21 podcast, "Punk Rock, Barbiturates, and Bipolar Disorder." Search for "Carlat" on your podcast store.

❖ ❖ ❖

Expert Interview

Continued from page 4

Ms. Eban: It's hard to connect the dots. How do you know if a bad outcome is due to a bad drug? Doctors who prescribe drugs with a narrow therapeutic index are more likely to make the connection. At the Cleveland Clinic, the transplant team figured out that their patients were suffering organ rejection after being switched to a certain Indian-manufactured immunosuppressant.

TCPR: What can clinicians do about this?

Ms. Eban: Clinicians usually don't know which generic their patient is taking. But if they have a patient who's suddenly become unstable, it might be worth finding out if the pharmacy dispensed drugs from a different manufacturer.

TCPR: Do any medications or manufacturers stand out?

Ms. Eban: I don't want to be in a position of calling winners and losers. But I get a lot of queries about that, so I've created a five-step guide at www.katherineeban.com/guide. Patients can start by finding out who manufactured their medicine. They can check if that manufacturer has run afoul of the FDA—namely, if there have been problems with sterility (ie, contamination) or data integrity (ie, fraud). If there are problems, patients can find another manufacturer from the FDA's Orange Book and request a change.

TCPR: What's next for you?

Ms. Eban: I have been investigating the Trump administration's response to COVID-19 for *Vanity Fair* magazine. Unfortunately, I'm going to be doing a lot more of that.

TCPR: Thank you for your time, Ms. Eban.

To learn more, listen to our 5/10/21 podcast, "What's Wrong With Generics? An Interview With Katherine Eban." Search for "Carlat" on your podcast store.

CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™ or 1 CE credit for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/
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. In a recent meta-analysis of pharmacotherapies for PTSD, which medication had the best balance of efficacy and acceptability (LO #1)?
   [ ] a. Venlafaxine [ ] b. Sertraline [ ] c. Prazosin [ ] d. Fluoxetine

2. What range of vitamin D levels is associated with the lowest risk of mortality (LO #2)?
   [ ] a. 12–20 ng/mL [ ] c. > 40 ng/mL
   [ ] b. 20–40 ng/mL [ ] d. 15–25 ng/mL

3. Over a period of four years, an FDA investigator inspected generic drug manufacturing plants in India and China, and found evidence of fraud in four-fifths of the plants (LO #3).
   [ ] a. True [ ] b. False

4. A 2020 study of patients with bipolar disorder found that maintenance therapy, compared to drug discontinuation, was associated with a lower recurrence rate of which mood episode subtype at 6 months (LO #4)?
   [ ] a. Depressive [ ] b. Manic [ ] c. Mixed [ ] d. All subtypes

5. Which of the following is a benefit of topiramate in PTSD (LO #1)?
   [ ] a. Topiramate is most beneficial for avoidance symptoms
   [ ] b. Topiramate has been shown to help irritability in PTSD more than core reexperiencing symptoms
   [ ] c. Topiramate has been shown to reduce the number of standard drinks per week in those with comorbid alcohol use disorder
   [ ] d. Topiramate does not impair cognition

Depression, Vitamin D, and COVID-19

Continued from page 5

Balance is key

We have some evidence that treating vitamin D deficiency may be good for physical and mental health, but what if we go too far? Several observational studies suggest that there is a point where high levels of vitamin D increase the risks of respiratory infection, cancer, and death. In terms of mortality, the sweet spot appears to be between 20 and 40 ng/mL, according to one large cohort study of nearly 250,000 individuals (Durup D et al, *J Clin Endocrinol Metab* 2012;97(8):2644–2652). These studies support the recommendations by the Institute of Medicine to define vitamin D deficiency as < 12 ng/mL and insufficiency as < 20 ng/mL.

Labs and treatment

Vitamin D is worthwhile to check when screening for causes of psychiatric disorders. However, given the uncertainties in the benefits and possible risks of over-supplementation, I would only start treatment when a patient's levels are clearly low (< 20 ng/mL; see Quick Facts table for dosing). Recheck labs 3–4 months after starting treatment, and stop treatment once stores are adequate (> 30 ng/mL). If risk factors for low vitamin D remain (indoor living, poor diet, depression), recheck levels about 6 months after stopping supplementation.

Vitamin D: Quick Facts

Lab order	25-hydroxy vitamin D (billing code E55.9)
Interpretation	Deficient: < 12 ng/mL (5% of population) Insufficient: 12–20 ng/mL (18%) Sufficient: 20–40 ng/mL
Treatment	For deficiency, start 2000 IU of vitamin D_3 (cholecalciferol) daily For insufficiency, start 1000 IU of vitamin D_3 (cholecalciferol) daily For other values, no supplementation needed

TCPR VERDICT: Low vitamin D is common in the general population, and even more so in psychiatric patients. Supplementation is worthwhile, and may help depression, if there is a clear deficiency (< 20 ng/mL).

To learn more, listen to our 5/24/21 podcast, "How COVID Affects the Brain." Search for "Carlat" on your podcast store.

THE CARLAT REPORT
PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Problems With Generics
May 2021

Next Issue:
Depression
June/July 2021

Learn more and search full archives online:
www.thecarlatreport.com

In Brief: Lamotrigine Gets a New Warning

A new warning now sits beneath the list of life-threatening allergic reactions that can happen with lamotrigine. The anticonvulsant is suspected of causing cardiac arrhythmias in susceptible patients by slowing ventricular conduction and widening the QRS. A similar warning has long been in effect with carbamazepine, and both drugs are thought to exert this effect through sodium channel blockade. The problem is distinct from QTc prolongation, another cause of arrhythmias, which is seen with antidepressants and antipsychotics but not with lamotrigine (Rudd GD and Sake JK, *Br J Clin Pharmacol* 2011;71(6):963).

The American Epilepsy Society pushed back against the labeling, citing a lack of clinical support for the warning, which was based on two in-vitro studies. However, I counted six case reports of ventricular arrhythmias on lamotrigine, and the problem is well documented in lamotrigine overdose (Dream A et al, *Am J Emerg Med* 2018;36(7):1324.e1–1324.e2). While that suggests the risk is real, it is likely uncommon, considering lamotrigine has been in widespread use since 1994.

The original warning from October 2020 advised clinicians to "avoid" lamotrigine in at-risk patients. Last month, the FDA lightened the language to recommend weighing the risks and benefits, in line with carbamazepine's labeling. Patients most in need of this risk-benefit consideration are those with cardiac conduction disorders (second- or third-degree heart block, bundle-branch blocks), ventricular arrhythmias, heart failure, ischemic or structural heart disease, and sodium channel disorders (eg, Brugada syndrome). Combining lamotrigine with other sodium channel blockers, such as carbamazepine, would be expected to increase risk for conduction delay.

TCPR'S TAKE: Lithium, carbamazepine, the antipsychotics, and now lamotrigine all carry warnings about cardiac arrhythmias, leaving valproate (Depakote) as the only mood stabilizer unmarked by this risk. No one is recommending routine EKGs before starting lamotrigine, but if your patient has known cardiac conduction delay or significant ischemic or structural heart disease, a friendly consultation with a cardiologist is advised.

—Chris Aiken, MD, and Sarah Rivelli, MD. Dr. Aiken and Dr. Rivelli have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Now on Twitter: Daily research updates from the editors of the Carlat Report. @CarlatPsych