The Carlat Psychiatry Report

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

VOLUME 6, NUMBER 2 WWW.THECARLATREPORT.COM FEBRUARY 2008

Novel Anticonvulsants: An Update on Efficacy

The newer anticonvulsants have at least one thing going for them. They're easier to prescribe than the older agents, because they are less toxic and therefore do not require serum blood levels.

Unfortunately, aside from Lamictal, none of these medications have any psychiatric indications, so any psychiatric use is, by definition, off-label. There's no problem with that, necessarily, because FDA approvals notoriously lag behind the clinical evidence, which may take a while to accumulate.

In this article, we'll review the clinical data on three of the most frequently used of the novel anticonvulsants: Trileptal (oxcarbazepine), Topamax (topiramate), and Neurontin (gabapentin). We cover Lamictal in this month's expert interview with Nassir Ghaemi.

Trileptal

First approved by the FDA for epilepsy in 2000, Trileptal is a very close cousin of Tegretol (carbamazepine); in fact, if you put the two molecules side-by-side, they look identical except for an extra oxygen atom in the middle tricyclic ring of Trileptal. One might hypothesize that since it looks like Tegretol, it must be as effective as Tegretol for bipolar disorder.

And yes, Tegretol is a proven treatment for bipolar disorder, and was recently approved by the FDA for the treatment of manic episodes in an extended-release form called Equetro (manufactured by Shire Pharmaceuticals). However, Tegretol in any form is rarely used as a first-line treatment because of poor tolerability (fatigue, nausea, dizziness) and especially because of the risk of life-threatening side effects such as leukopenia, agranulocytosis, and liver failure. In addition, Tegretol is complicated to prescribe because it induces the synthesis of several P450 enzymes and may change the levels of concurrent medication; furthermore, it is metabolized by some of the same enzymes it induces, leading to unpredictable dips in its own serum level.

Trileptal, on the other hand, is free of most of these problems. Fatigue and dizziness may occur, but tend to be milder. It leaves both white blood cells and the liver alone. And although Trileptal does mildly induce P450 3A4, and thus can reduce levels of oral contraceptives and calcium channel blockers, it does not induce its own metabolism, making it easier to titrate. Because it has a broad therapeutic index, and because there is no known therapeutic level, Trileptal serum levels are unnecessary; the only laboratory monitoring needed is a couple of serum sodium levels during the first 3 months of treatment, since it causes significant hyponatremia in 2.5% of patients (according to the PDR).

What about Trileptal's efficacy – does it work for bipolar disorder as well as Tegretol? Probably not, but the data are so scant that it's hard to know for sure. Two controlled trials conducted in Germany in the early 1980s showed that Trileptal was as effective as both Haldol and lithium for the treatment of acute mania (Emrich HM, *Int Clin Psychopharmacol* 1990; 5 (Suppl.): 83-88), but the numbers were small and the outcome measures used were unfamiliar to current-day researchers.

Most of the studies since then have been either retrospective chart review studies or case series in which patients with refractory bipolar disorder were given adjunctive Trileptal. The results of these pilot studies have generally been positive. For example, one study enrolled 20 treatment-resistant bipolar I patients, and added Trileptal to their current mood stabilizers, titrated to a mean dose of 930 mg/day. After 3 to 6 months, 7/20 patients (35%) had responded or remitted (Conroy CR et al., *J Clin Psychopharm* (letter) 2006;26:95-97).

Such uncontrolled studies are difficult to get all that enthusiastic about, since the positive responses may be due to the placebo effect or natural remission. Recently, two controlled studies have been published. One randomly assigned 30 patients with hypomania to either Depakote (divalproex

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  The Use of Lamictal in Psychiatry

Learning objectives for this issue: 1. Evaluate the clinical evidence regarding the use of novel anticonvulsants in psychiatry. 2. Describe the evidence-based indications for the use of Lamictal in mood disorders. 3. Identify the utility of the kindling hypothesis.

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.

Novel Anticonvulsants: An Update on Efficacy

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sodium) or Trileptal, and both meds were equally effective, although this was only a single-blind study (the only person blinded to the medication was the symptom rater) (Suppes T et al., *Aust NZ J Psychiatry* 2007;41(5):397-402).

Unfortunately, the only truly gold standard study to be published on Trileptal in psychiatry showed it to be a miserable failure. This multicenter trial randomized 116 children and adolescents (ages 7-18) with bipolar disorder to either Trileptal (mean dose 1515 mg/day) or placebo. After 7 weeks of double blind treatment, Trileptal improved the Young Manic Rating Scale score by 10.9 points, versus placebo's improvement of 9.8 points. This difference was not statistically significant (Wagner KD et al., *Am J Psychiatry* 2006; 163:1179-1186). Of course, one can reasonably argue that pediatric bipolar disorder is very different from adult bipolar; nonetheless, most psychiatrists treat the two populations the same way, with mood stabilizers and atypical antipsychotics.

Ultimately, Trileptal is one of those third-line drugs that one might add as adjunctive treatment when nothing else is working. Most prescribers start at 150 mg QHS or BID, and gradually increase (over a week or two) to about 600 mg BID. Warn patients about transient dizziness and nausea, inform them that their oral contraceptives and calcium channel blockers may need a dosage increase, and get sodium levels at 4 and 12 weeks. Common symptoms of mildly decreased sodium are fatigue and ankle edema, and both Gatorade and milk are good sources of extra sodium. Generally, Trileptal does not cause significant weight gain.

Topamax

Topamax (topiramate) is approved by the FDA for epilepsy and migraine headaches, but has been used as an off-label medication for bipolar disorder. When we last looked at the Topamax data in psychiatry (*TCPR*, Sept 2003), we concluded that it was probably effective, based on several open-label trials. Since then, several placebo-controlled trials have been published, and they have not been kind to Ortho-McNeil, the manufacturer.

A good place to start a review of this literature is to read a paper written by the manufacturers of Topamax in which they present the results of four separate placebo-controlled trials of Topamax for acute mania. In all four of the studies reviewed, Topamax was no better than placebo, and in the two studies that included lithium as an active comparator, lithium was more effective than both Topamax and placebo (Kushner SF, et al., *Bipolar Disorder* 2006;8:15-27). Ouch.

These studies tested the use of Topamax *monotherapy* for mania, not a practice that most psychiatrists are likely to use. What about the common practice of adding Topamax to standard mood stabilizers in order to boost response? Several open trials had reported that adjunctive Topamax, titrated up to about 250 mg/day, resulted in improvements in mania, hypomania, or mixed episodes in 50-60% of patients (see, for example, McElroy SL et. al., *Biol Psychiatry* 2000; 47:1025-33). But, again, what looked fairly effective in open trials turned out to do poorly in placebo-controlled, double-blind trials. In one study, for example, 287 patients with Bipolar I Disorder with either manic or mixed episodes, all of whom were already taking either lithium or Depakote, were randomly assigned to either adjunctive Topamax (mean dose, 255 mg/day) or adjunctive placebo. There were no significant differences between Topamax and placebo in any of the efficacy measures used (Chengappa R, et al., *J Clin Psychiatry* 2006;67:1698-1706). Similar negative results were reported in a placebo-controlled trial of adjunctive Topamax for patients with Schizoaffective Disorder, bipolar type (Chengappa R, et al., *Bipolar Disorder* 2007;9(6):609-617).

Okay, so it doesn't work for psychiatric symptoms. It causes weight loss as a side effect, so why not at least add it to help our patients lose weight? One study looked at this use specifically, randomly assigning overweight patients with bipolar disorder to adjunctive open label treatment with Topamax or the approved weight loss medication Meridia (sibutramine). Weight loss was comparable in the two groups, with an average of nearly 2 pounds of weight loss per week. Unfortunately, the drop-out rate was so high (about 80% in both arms of the study), that the ultimate amount of weight loss achieved was not very high (an average of 6-9 pounds over 24 weeks) (McElroy SL, et al., *Bipolar Disorder* 2007;9(4):426-434).

If you do choose to use Topamax even after our poor review, be aware of its side effects, including sedation (29% listed prevalence in the PDR), psychomotor slowing (13%), memory loss (12%) and confusion (11%). These side effects have earned the medication the nickname "Dopamax." An odd side effect of Topamax is the development of kidney stones in 1-2% of patients taking it, which is about 3 times higher than the rate in the general population. This is apparently caused by the fact that Topamax is a weak carbonic anhydrase inhibitor. Finally, Topamax is a weak 3A4 inducer, and can decrease the levels of oral contraceptives, a dangerous problem.

Neurontin

It's hard to know what to make of Neurontin (gabapentin), which is approved by the FDA for epilepsy and postherpetic neuralgia. From a political perspective, Neurontin is a lightning rod for critics of the excesses of pharmaceutical industry marketing, since the original manufacturer, Warner Lambert, pleaded guilty to having illegally marketed it for a variety of off-label indications, including bipolar disorder. The company had to pay a fine of nearly half a billion dollars.

Regulatory issues aside, does Neurontin work for anything we are likely to encounter in our practices? Well, we can be pretty certain that it does not work for bipolar disorder, since two placebo-controlled trials were negative (Pande AC, et al., *Bipolar Disorder* 2000;2:249-255, and Frye MA, et al., *J Clin Psychopharmacology* 2000;20:607-614). Many clinicians like to try Neurontin for patients with anxiety and insomnia, since it is not addictive. Two placebo-controlled studies have been done, one for panic disorder, and the other for social phobia.

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