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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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IN THIS ISSUE

Focus of the Month:
Anticonvulsants 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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The Kindling Hypothesis: Is It Relevant in Psychiatry?

Over the past couple of decades, psychiatry has adopted a number of anticonvulsants that effectively treat psychiatric conditions. The "kindling hypothesis" has provided a rationale for their increasing use, but what is the evidence behind this theory, and is it actually applicable for psychiatric practice?

The phenomenon of kindling was first discovered in 1967 by a scientist in Halifax, Nova Scotia, named Graham Goddard. Goddard was a neuroscientist interested in the neurobiology of learning. In one series of experiments, he electrically stimulated various regions of rats' brains to observe the effects on their ability to learn tasks. In repeating these stimulations daily, he discovered something unexpected: the rats began having seizures in response to stimuli that would normally be too low to provoke seizures. Ultimately, many of the rats began having unprovoked seizures. Somehow, Goddard had created epileptic rats.

He eventually called this phenomenon "kindling" (Goddard GV, Development of epileptic seizures through brain stimulation at low intensity, *Nature* 1967;214:1020). Just as a large log will not burn unless kindled by the combined action of small twigs burning, it appeared that epilepsy required a similar kind of kindling by a sequential series of small electrical stimuli.

How does this relate to psychiatry? The most common analogy is between an epileptic seizure and a manic episode of bipolar disorder. Like seizures, manic episodes can occur without obvious triggers, and have fairly abrupt beginnings and endings. In the case of bipolar disorder, the "kindling" is theoretically provided by stressful life events, which may produce certain kinds of electrical brain stimulations. At first, these events are not sufficient to cause a manic episode, but over time, they may accumulate to trigger such an episode. Furthermore, "episodes may beget episodes," meaning that the manic episodes themselves may damage the brain in some way, making it more vulnerable, so that eventually the episodes may begin to occur spontaneously, without a trigger.

The evidence for kindling in bipolar disorder is indirect. The most eloquent spokesperson – indeed, the person who initially applied the idea of kindling to psychiatric illnesses – is Robert Post, who is currently a professor of psychiatry at George Washington University. In a recent paper, he concisely reviews the evidence for kindling in affective disorders (Post R, *Neuroscience and Biobehavioral Reviews* 31 (2007) 858-873). He cites studies showing that patients who have had a number of affective episodes are more vulnerable to future episodes – and that later episodes are less likely to require an environmental trigger than earlier episodes. But he acknowledges that some studies disagree, and that many patients do not follow these patterns.

Skeptics would argue that studies cited as evidence of kindling may simply be identifying a subset of patients with severe affective illness who get worse over time, as do many severely ill patients in all of medicine. True, one possible explanation of worsening over time is that the prior episodes do some cumulative damage ("episodes begetting episodes") but there are many other equally plausible explanations: an underlying disease of neurotransmitters may worsen with time and be unrelated to kindling; severely psychiatrically ill patients make a series of poor life decisions that lead to vicious cycles of more stress triggering more illness, and so on.

If the kindling hypothesis were true, what are the clinical implications? The major one is that you should treat early and aggressively, in order to prevent the pathological affective episodes. But again, this clinical wisdom is hardly dependent on the kindling hypothesis, and most clinicians would agree that aggressive treatment of psychiatric illness is warranted, regardless of the hypothesized cause.

Perhaps the most misunderstood aspect of kindling is that it implies that we should treat affective disorders with the same medications as are used for epilepsy. In fact, in the words of Dr. Post, "We…use the kindling model only for its heuristic value in asking questions regarding the longitudinal course of illness and response to treatment. The utility of this model must ultimately rest on its indirect or clinical predictive validity (Post RM, et al., *Clinical Neuroscience Research* 2001;1:69-81)." In an email to me, Post pointed out that another big misunderstanding of the kindling hypothesis is that it means that affective illness progresses relentlessly. "Not true," he said. "If you treat it aggressively enough any point in its course, you can hopefully stop it."

TCPR VERDICT:

Kindling: Not a roadmap for treatment decisions

Q&A With the Expert

This Month's Expert:

S. Nassir Ghaemi, M.D.

Lamictal in Bipolar Disorder

Associate Professor of Psychiatry and Public Health
Director, Bipolar Disorder Research Program
Emory University School of Medicine

Dr Ghaemi has served on the advisory boards of GlaxoSmithKline, Janssen, Pfizer, Shire, and Abbott Laboratories, receives research grants from GlaxoSmithKline and Pfizer, and serves on the speakers' bureaus of GlaxoSmithKline, Astra Zeneca, Pfizer, Janssen and Abbott Laboratories.

TCPR: Dr. Ghaemi, Lamictal (lamotrigine) has become a very popular medication in psychiatry, but there remains some confusion about when to use it. What is its official FDA-approved indication?

Dr. Ghaemi: Lamictal is approved for delaying the time to relapse to depressive and manic episodes in bipolar type I disorder. This is based on two good randomized clinical trials. They were both 18-month studies. One of them began with the patients being depressed, and the other one began with the patients being manic. In the first study, patients with acute bipolar depression were all given Lamictal open-label, and patients who responded to Lamictal (about half of the subjects) were then enrolled in the double-blind part of the study, in which they were randomized to Lamictal, lithium, or placebo (Calabrese JR, et al., *J Clin Psychiatry* 2003 Sep;64(9):1013-24).

TCPR: And what were the results of that study?

Dr. Ghaemi: Compared to placebo, Lamictal and lithium prolonged the time to a recurrence of depression and mania.

TCPR: I know you have some reservations about the methodology used in the Lamictal studies – what are they?

Dr. Ghaemi: Patients were eligible for the study only if they had tolerated and responded to Lamictal, meaning that the study sample was enriched with patients who were likely to do well on that agent.

TCPR: In other words, the deck was stacked in favor of Lamictal. Is that an unusual study design?

Dr. Ghaemi: Actually, it isn't unusual. All maintenance studies in bipolar disorder these days are done this way. For example, both the Zyprexa studies and the Abilify studies, both of which got FDA approval, used the same method: patients were preselected based on whether their acute mood episode responded to the drug of interest, then they were enrolled in double-blind trials comparing that drug with placebo.

TCPR: Why is this design so popular?

Dr. Ghaemi: There are two rationales behind it. First, if you want to maximize the likelihood that the drug will be better than placebo, then this would be one way of doing it. There were previous studies in which this approach was not taken, like the Depakote maintenance study (Bowden CL et al., *Arch Gen Psych* 2000;57:481-489). In that case the study was not enriched with Depakote responders; people were allowed to be in the study even if they hadn't taken Depakote before. They were enrolled if their bipolar disorder was in remission, and then they were randomized to Depakote, lithium or placebo, and followed for a year. In the end, Depakote and lithium were not better than placebo, and so the FDA did not give Depakote an indication for maintenance treatment of bipolar disorder. The second rationale is that this design more accurately reflects clinical practice. Psychiatrists don't wait until people are in remission before trying a medication; instead, they start these drugs during an acute episode of depression or mania, and then they need to decide whether or not to continue patients on the drug long-term.

TCPR: So what are the problems with this design?

Dr. Ghaemi: The disadvantages are two-fold. One is that even if the data are valid they do not generalize to all patients. In other words, what studies like this show is not that you can put anybody on Zyprexa or Abilify or Lamictal and they will have long-term benefits in bipolar disorder. What they show is that if somebody does well with those drugs for an acute episode, they might do well with those drugs long-term. The second critique is that this design does not fairly compare Lamictal with lithium because the patients were preselected to be tolerant of and responsive to Lamictal but they were not preselected to be tolerant of and responsive to lithium. So it shouldn't be a surprise that in some of the analyses, Lamictal is better tolerated and more effective than lithium.

TCPR: So, according to your reading of the data, what is the clinical situation that we should be using Lamictal for?

Dr. Ghaemi: It should help more than placebo with the prevention of both mania and depression, although probably more effectively for depression than mania. This benefit is best seen in persons who initially tolerate and appear to benefit from Lamictal acutely.

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Q & A With the Expert

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TCPR: It seems to me that many clinicians have jumped to the conclusion that since Lamictal works to prevent depression, therefore it must also be effective for treating an acute episode of depression.

Dr. Ghaemi: And that makes intuitive sense, but you can never assume that just because a drug is effective for prevention of depression that it is also effective for acute treatment, or vice versa. I call it "the happily ever after fallacy," this idea that if you get better acutely, you are going to stay better forever if you just stay on the same drug. For instance, quetiapine works for acute bipolar depression but we don't have data to show that it prevents it. And there is extensive literature on lithium for depression prevention in bipolar disorder but much less definitive literature for acute efficacy.

TCPR: What is the actual evidence with regard to Lamictal for treating acute depression, either bipolar depression or unipolar depression?

Dr. Ghaemi: Five studies have been conducted testing Lamictal for acute bipolar depression and two for unipolar depression. Each had a similar design with adequate numbers of subjects (about 200 per study), and every single one of these studies was negative, meaning that Lamictal performed no better than placebo.

TCPR: That's surprising. Have these studies all been published?

Dr. Ghaemi: Only one was published, and that was a study in which a secondary analysis showed that Lamictal was more effective than placebo (on the MADRS depression scale), but there was no separation on the primary outcome (the Hamilton depression scale) (Calabrese JR et al., *J Clin Psychiatry* 1999;60:79-88).

TCPR: How do you know about the results of the other studies if they were never published?

Dr. Ghaemi: Because GlaxoSmithKline was legally required to post all of their studies, positive or negative, on their website (see http://ctr.gsk.co.uk/Summary/lamotrigine/studylist.asp). This was a result of an earlier suit accusing the company of suppressing data that indicated a significant suicide risk among children taking Paxil.

TCPR: Does this data mean that Lamictal is actually not an effective antidepressant?

Dr. Ghaemi: I think that is the obvious conclusion, at least acutely. When there are that many well-powered studies, and all are negative, this usually means the drug doesn't work. However, there is one other interpretation if one wanted to be more charitable, which is based on the fact that Lamictal requires a very slow titration – most of these studies were about two months long and it takes a month just to get to 100 mg, which would be an average dose. Maybe Lamictal didn't have enough time to show a benefit, and maybe a 12 or 16 week study would have shown a separation from placebo. The problem is that the average major depression episode in bipolar disorder gets better naturally in three to six months. So there is no way you could prove it; you couldn't make the study longer and show that Lamictal is better than placebo because the placebo recovery would be very high. So either Lamictal is an ineffective antidepressant, or it is effective but irrelevant, because by the time it would work the present episode would disappear naturally.

TCPR: My sense is that very few people know about these negative data, is that true?

Dr. Ghaemi: It is true. I first came across this data about a year ago, and I actually serve on the national advisory board for Lamictal, so I am privy to more data than most psychiatrists.

TCPR: I think most psychiatrists would assume that somebody being paid by the company to be on an advisory board would be biased in favor of the product, or at least unlikely to blow the whistle on negative studies. Are you unusual in that sense?

Dr. Ghaemi: I think I am in the minority. My experience in the few advisory boards that I have been on is that it is not uncommon for there to be one or two people in that room who are pretty critical of the company's approach about interpreting or marketing their data. So to some extent the companies are willing to hear criticism, but usually it is a minority view that ultimately doesn't have much impact on what they decide to do.

TCPR: My understanding is that you wrote up your discovery of the negative Lamictal data and submitted the paper to some journals. What has been the response?

Dr. Ghaemi: I first submitted it to *JAMA* because I knew that they were sympathetic to this kind of critique. Their reaction was, "We already publish many papers like this; this is old news; there is nothing new here." They recommended that I send it to a psychiatric journal. So then I sent it to the *American Journal of Psychiatry*, but they rejected it as well, saying that they were doubtful that this type of negative publication bias was common among other companies marketing medications for bipolar disorder.

TCPR: Do you think there is much suppressed negative data about other drugs?

Dr. Ghaemi: It's very hard to get this information. Companies are not required to disclose it. And if they do publish it, they will sometimes delay publication for two or three years, and then publish it in an obscure journal that is less likely to be read.

Research Updates IN PSYCHIATRY

PRACTICE ISSUES

DEA changes rules to allow post-dating of schedule II substances

In a ruling certain to make psychiatrists and their patients happy, the DEA has finally said that doctors may give patients 90 days worth of prescriptions for schedule II controlled substances, which includes stimulants and narcotics. Before this ruling, we were formally required to have all our ADHD patients come for monthly visits in order to get their stimulant prescriptions. Of course, few of us actually did this, and post-dating scripts has become standard practice for stable patients who have continued on the same dose of the same medication for the long term. With this ruling, issued on December 19, 2007, we are finally no longer breaking the law. See http://www.deadiversion.usdoj.gov/fed_regs/rules/2007/fr1119.htm

TCPR's Take: Check with your state's board of pharmacy website (see the following site for a comprehensive listing of all board of pharmacy websites: http://www.edhayes.com/sbp-main.html). Not all states have to agree with this federal ruling, and in states where the controlled substance laws are more restrictive, you may not be able to take advantage of the DEA's new policy.

AGGRESSION

Placebo more effective than antipsychotics for aggression in mental retardation

In a multi-center study conducted in Great Britain and Australia, 86 adults with mental retardation (IQ < 75) and aggressive behavior were randomized to double-blind treatment with Risperdal (mean dose, 1.8 mg/day), Haldol (mean dose, 2.9 mg/day), or placebo. The primary outcome was score on the modified overt aggression scale (MOAS) at 4 weeks. The results were that placebo reduced the MOAS score by more than either of the active treatments, with the difference close to being statistically significant ($p=.07$ vs. Risperdal and $p=.06$ vs. Haldol) (Tyrer P, et al., *Lancet* 2008;371(9606):57-63).

TCPR's Take: These results are different from some prior studies which showed a benefit of Risperdal in this population. One likely reason is that past studies included a "placebo run-in" phase, in which patients who responded rapidly to placebo were excluded from the double-blind study. This had the effect of minimizing the placebo effect in the main study and increasing the likelihood of a drug vs. placebo difference. These investigators did not include the placebo run-in in order to make the design more similar to clinical practice. These results imply that in aggressive mentally retarded adults, placebo effects are extremely powerful, and perhaps prescribing a multivitamin (with great fanfare and high expectations) is as effective as prescribing an antipsychotic, with far fewer side effects.

PSYCHOSIS

Criteria proposed to predict which prodromal patients will become psychotic

The North American Prodrome Longitudinal Study is a consortium of 8 academic centers (all but one in the U.S.) seeking to develop predictors of the development of psychosis in young patients who present with prodromal symptoms. Using the Structured Interview for Prodromal Syndromes (SIPS), researchers identified 291 subjects who met criteria for a "prodromal syndrome." Most of the subjects meeting the prodromal critiera had "attenuated positive symptoms." Psychotic symptoms were defined as "attenuated" when patients were not completely convinced of the veracity of their delusions or hallucinations. The researchers then followed prodromal subjects for 2 ½ years to see who would develop full-blown psychosis. The overall risk for conversion to psychosis over this time period was 35%. The investigators scanned their data in search of factors that were predictive. The most accurate predictions (74-81%) occurred when combining three factors: genetic risk for schizophrenia plus recent functional decline, unusual thought content, and either suspicion/paranoia or impaired social functioning (Cannon TD et al., *Arch Gen Psychiatry* 2008;65(1):28-37).

TCPR's Take: These results garnered a fair amount of media attention, with headlines such as "Scientists Can Predict Psychotic Illness in up to 80 Percent of High-Risk Youth" (from NIH's press release). But when you actually look at the study, these results are neither particularly surprising nor very clinically useful. In order to be enrolled, patients were pretty close to being psychotic already, with significant psychotic ideation, defined as "prodromal" by the researchers. Chances are that most of these prodromal patients would have received treatment for psychosis if they had shown up in your office or mine. On the plus side, the study reminds us of the importance of certain factors, such as family history of schizophrenia and deteriorating social functioning, that we should make sure to explore systematically in at-risk patients.

PHARMACOGENOMICS

New lab test recommended before prescribing Tegretol or Lamictal to Asians

The FDA has issued a warning that Asian patients with a specific human leukocyte antigen (HLA) are at increased risk of developing life-threatening Stevens Johnson syndrome rash, and should be tested for this antigen before initiating treatment. The HLA in question is identified as "HLA-B 1502." About 10% of Asian people have this allele, according to the FDA. Patients who are HLA-B 1502 positive should be prescribed Tegretol only if the potential benefits far outweigh the risks. While the FDA's warning focuses on Tegretol, it does mention that other anticonvulsants associated with SJS should be accorded the same treatment, and this would include Lamictal (lamotrigine). (The FDA alert can be accessed at http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm.)

CME Post-Test

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Please identify your answer by placing a check mark or an X in the box accompanying the appropriate letter.

1. A recent placebo-controlled study of Trileptal found:
- [ ] a. It is ineffective for bipolar disorder in adults.
- [ ] b. It is ineffective for bipolar disorder in children.
- [ ] c. It is more effective than Lamictal for depression.
- [ ] d. It is less effective than Depakote for bipolar disorder.

2. Evidence consistent with the kindling hypothesis includes:
- [ ] a. Both lithium and Depakote are effective for mania.
- [ ] b. Some bipolar patients improve spontaneously as they age.
- [ ] c. Mood episodes sometimes increase in frequency with age.
- [ ] d. Psychosocial stressors often trigger mood episodes.

3. Asian patients with HLA-B 1502 are at higher risk for Stevens Johnson Syndrome due to Tegretol.
[ ] a. True [ ] b. False

4. Lamictal is FDA-approved for:
- [ ] a. Treatment of acute depression.
- [ ] b. Treatment of acute mania.
- [ ] c. Prevention of a mood episode relapse in bipolar disorder.
- [ ] d. Adjunctive treatment with lithium or Depakote.

5. According to Dr. Ghaemi, unpublished studies of Lamictal for mood disorders have been positive.
[ ] a. True [ ] b. False

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1. Did the content of this activity meet the stated learning objectives? [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME/CE activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

Novel Anticonvulsants: An Update

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We reviewed both these studies in the March 2003 issue of *TCPR*. The results were not completely negative, but they were not very impressive, either.

The drug does seem to have picked up some steam as a treatment for some symptoms of recently abstinent alcoholics, especially insomnia. For example, researchers at the University of Michigan reported an open trial of Neurontin vs. trazodone for insomnia in newly sober alcohol-dependent patients. Out of 50 outpatients consecutively referred to a clinic, 34 were treated with Neurontin (mean dose, 888 mg/bedtime) vs. 16 with trazodone (105 mg/bedtime). Both medications led to significant improvement in sleep after 4-6 weeks (Karam-Hage M, et al., P*sychiatry and Clin. Neurosciences* 2003;57:542-544).

One rather backhanded endorsement of Neurontin's anti-anxiety potential was implied in a recent letter to the editor of the *Journal of Clinical Psychiatry*. The authors reported two cases of alcoholic patients who abused Neurontin and then developed symptoms similar to delirium tremens upon withdrawal (Pittenger C and Desan P, *J Clin Psychiatry* (letter) 2007;68:483-484). If the medication is that well-loved by alcoholic-dependent patients, one assumes that it provides some sort of tranquilization.

TCPR VERDICT: ***Novel anticonvulsants: Efficacy questionable, but sometimes worth a try.***

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This Month's Focus:
Anticonvulsants in Psychiatry

Next Month in *The Carlat Psychiatry Report*: Update on Substance Abuse Treatment, including reviews of the latest medication and psychosocial treatment options.