The Carlat Psychiatry Report

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

VOLUME 6, NUMBER 7&8 WWW.THECARLATREPORT.COM JULY/AUGUST 2008

Antidepressants and Bipolar Disorder: An Update

Much of what is confusing and controversial in the treatment of bipolar disorder revolves around the role of antidepressants. Are they dangerous or safe? Are they effective or ineffective? Does it matter whether the patient has Bipolar I or II?

Do antidepressants cause manic switching?

In some circles, even asking this question is tantamount to asking if the earth is round. Manic switching seems to be something we see frequently in our clinical practice. The problem is that appearances can be deceiving. Bipolar disorder is, by definition, a cycling condition. If a bipolar patient becomes manic after being put on an antidepressant, a cause-effect relationship may be inferred when, in fact, this may be a part of the natural course of the patient's illness, unrelated to the antidepressant.

An older, chart review study, though limited methodologically, makes this basic point clearly (Lewis and Winokur, *Arch Gen Psychiatry* 1982; 39(3):306). The authors reviewed medical charts of 27 bipolar patients who had received no treatment, versus 26 patients who had received treatment with tricyclics. Patients who did not receive treatment had a 41% switch rate, vs. a 28% switch rate in treated patients. While we can't read too much into the numbers of this observational study, it is a good reminder that the natural history of bipolar disorder is one of shifting mood states, with or without antidepressants on board.

In order to validly answer the question of whether ADs cause manic switching, it is necessary to compare switch rates on ADs to switch rates on placebo. The placebo group provides an estimate of the spontaneous switch rate, allowing us to interpret the significance of switch

Continued on Page 3

IN THIS ISSUE

Focus of the Month:
Bipolar Disorder

Lamictal: What is it Good For?

Lamictal (lamotrigine) is immensely popular among American psychiatrists. A recent survey found that it is prescribed more frequently than any other mood stabilizer (*Clin Psychiatry News*, June 2008, page 1). Now that psychiatrists have become so comfortable with prescribing it, a disturbing question is gradually emerging from the fog of therapeutic enthusiasm. Is Lamictal actually effective?

True, it is approved by the FDA for bipolar disorder, but here is the precise wording, taken from the package insert: "Lamictal is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of Lamictal in the acute treatment of mood episodes has not been established."

In other words, the FDA is saying that Lamictal is effective only when prescribed to patients who are *already* euthymic — neither depressed nor manic. We've known for some time that the drug does not outperform placebo in quelling the symptoms of mania, although it is extremely hard to find the details of these studies. Most references to the data cite a poster presentation from a meeting (Bowden et al., 39th Annual ACNP Meeting, 2000).

In February of this year, we interviewed Nassir Ghaemi about the unpublished data showing that Lamictal is ineffective

Continued on Page 2

Learning objectives for this issue: 1. Discuss the latest data on the use of antidepressants in bipolar disorder. 2. Describe controversies related to the overdiagnosis or underdiagnosis of bipolar disorder. 3. Describe situations in which prescribing Lamictal is appropriate. 4. List the weight gain liabilities of the various mood stabilizers. 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.

Lamical: What Is it Good For?

Continued from Page 1

for the treatment of bipolar depression (*TCPR* Feb 2008, p. 4-5). Shortly thereafter, GSK finally published the negative Lamictal data they have been accumulating.

Let's take a look at this new paper for what it might teach us about how Lamictal should or should not be used (Calabrese et al., *Bipolar Disorders* 2008;10:323-333). This is a review of the results of all five GSK-funded controlled trials of Lamictal for bipolar depression. According to another recent paper, these studies took place between 1996 and 2001 (Weisler et al., *J Affect Disorders* 2008;108:1-9).

The trials lasted from 7 to 10 weeks and all were placebo-controlled and double-blind. In total, they randomly assigned 607 patients to Lamictal, and 531 to placebo. The dose of Lamictal ranged from 50 mg/day to 400 mg/day, with the majority of patients gradually titrated to 200 mg/day. By and large, these patients had bipolar I disorder, and had moderate to severe depression on study entry. Exclusion criteria varied a bit, but all studies excluded rapid cyclers and those with prior Lamictal treatment. The primary outcome variable in two of the studies was the change in score from baseline to endpoint on the 17-item HAM-D (Hamilton depression scale), and for three of the studies was the change on the MADRS (Montgomery-Asberg Depression Rating Scale).

What were the results? There were no significant differences between Lamictal and placebo in any of the primary outcome variables for any of the five studies. In one study, however, some of the secondary outcome variables showed a significant benefit of Lamictal. The authors stress that patients in these studies demonstrated unusually high placebo response rates (from 35% to 48%, as estimated from bar graphs in the paper), and this may have led to the lack of separation between Lamictal and placebo. This is somewhat convincing. For example, the placebo response rates in the pivotal bipolar depression Seroquel trials were 36% to 37%, within range of the Lamictal placebo rates but certainly at the lower end of the scale (Calabrese, et al., *Am J Psychiatry* 2005).

So where does this leave us? According to the highest quality data, Lamictal is ineffective for the acute treatment of both manic and depressed episodes of bipolar disorder. The problem is that most clinicians will swear up and down that their depressed patients have, in fact, responded to Lamictal. Some of these responses must be placebo responses. However, consider an open label 16 week comparison of Lamictal and lithium. Researchers randomized patients with bipolar II depression to treatment with either Lamictal (N = 44, titrated to 200 mg/day) or lithium (N = 54, serum level 0.6-1.2 mEq/L) and followed them for 16 weeks (Suppes et al., *J Affect Disord* 2008, online version). This was a single-blind trial, in which only the raters were blinded to the treatment, and there was no placebo arm. Both treatments were effective: patients on Lamictal had a 67.5% response rate, and patients on Li, a 55.1% response rate (the difference was not statistically significant).

Lamictal Dosing Guidelines

Usual Dosing 25 mg QD X 1 week, increase by 25 mg per week

Dosing with Depakote or in patients with a history of any drug rash: 12.5 mg QD X 1 week, increase by 12.5 mg per week

Rash risk is maximal during first few months of treatment

Why is this study important? Because one of the explanations offered for Lamictal's generally poor performance in trials for depression is that its gradual titration requirement prevents it from achieving a therapeutic level within the time frame of short-term studies. This study, however, lasted 16 weeks, and while patients on Lamictal showed some improvement after 8 weeks, this improvement increased over the ensuing 8 weeks.

Thus, Lamictal may, indeed, be effective for bipolar depression, but only if continued for a long period of time. And this is likely why it performed better than placebo in the 18 month-long maintenance trials that led to FDA approval. True, it wasn't shown to actually improve depression in these trials, just to delay it, but you might speculate that if the drug had been tested against placebo for 18 months for depression treatment, it *might* have shown an advantage.

So what's the bottom line for this complicated but popular drug? If you decide to use it for acute depression, it may work, but don't expect miracles quickly. Depending on where you stand on the issue of antidepressant safety in bipolar disorder, consider accompanying Lamictal with a quick burst of standard antidepressant treatment. Once the patient has stabilized, you can discontinue the antidepressant, leaving Lamictal on board to do its maintenance magic. If you are in the anti-antidepressant camp, then try Seroquel, now FDA-approved for bipolar depression. But the common side effects of this atypical antipsychotic — weight gain and sedation — continue to make it a less-than-attractive option.

TCPR VERDICT: ***Lamictal: Probably helps, but patience required***

Antidepressants and Bipolar Disorder: An Update

Continued from Page 1

rates on antidepressants.

In 2004, a meta-analysis was published reviewing 12 placebo-controlled clinical trials in which patients with bipolar depression were randomly assigned to antidepressants vs. placebo or other active treatments (Gijsman et al., *Am J Psychiatry* 2004;161:1537-1547). Of the 12 studies, 5 reported manic switch rates, and in these studies the overall manic switch rate for patients on antidepressants was 3.8% (11 out of 287 patients) and for patients on placebo, it was 4.7% (23 out of 492). This suggests that antidepressants do not cause manic switching. Of note, most patients were on mood stabilizers as well as an antidepressant.

The researchers wondered whether the low overall switch rate might mask differences between types of antidepressant. They found three trials which compared the rates of manic switches for patients taking tricyclics vs. those taking SSRIs. The switch rate was 8% for tricyclics and 0% for SSRIs (not statistically significant due to low sample sizes). Overall, this meta-analysis suggests that SSRIs do not cause manic switching when patients are on concomitant mood stabilizers. The data is not as clear for tricyclics.

In the largest placebo-controlled trial of antidepressants for bipolar depression, 366 patients with bipolar depression were randomly assigned to mood stabilizer plus antidepressant, or mood stabilizer plus placebo. The researchers chose the two antidepressants widely considered the least likely to lead to manic switches, namely, paroxetine and bupropion. After 26 weeks of treatment, the manic switch rates were nearly identical in the two groups: 10.7% in the placebo group and 10.1% in the antidepressant group (Sachs GS, et al., *NEJM* 2007;356:1711-1722). There may be some problems with the generalizability of these findings, however, which we'll discuss in more detail when we talk about the surprising efficacy results of this study.

In another large clinical trial, 159 patients with bipolar depression (all of whom were taking mood stabilizers) were randomized in a double-blind protocol to receive adjunctive treatment with Wellbutrin (bupropion, mean dose, 286 mg/day), Zoloft (sertraline, 192 mg/day), or Effexor (venlafaxine, 195 mg/day). The patients were followed for 10 weeks, and some entered into a continuation treatment arm that went on for up to a year. There were no significant differences in the switch rates to mania or hypomania among any of the three antidepressants, with the overall switch rate being 19.3% at 10 weeks (Leverich et al., *Am J Psychiatry* 2006;163:232-239). Of course, since this trials was not placebo-controlled, it is hard to understand how to interpret this percentage. If a placebo arm had been included, patients taking placebo may have had a comparable spontaneous switch rate.

In a post-hoc analysis, the researchers reported that venlafaxine had a significantly higher threshold to subthreshold switch ratio than bupropion or sertraline. Unfortunately, the authors do not explain what the clinical meaning of this ratio might be. Nonetheless, they conclude that venlafaxine is more likely to lead to manic switching than bupropion or sertraline.

In sum, the placebo controlled data indicates that antidepressants (when added to a mood stabilizer) do not cause manic switching, and that we may be fooled by our preconceptions in our clinical practices. As always, of course, patients who enroll in randomized studies are not necessarily representative of the patients we see in the office, who may have more severe illness and more comorbid conditions.

Antidepressant monotherapy for bipolar disorder II

What about treating bipolar disorder with antidepressant monotherapy? Most of us would avoid this practice, in part because most treatment guidelines discourage it, but is it as dangerous as feared?

The Gijsman meta-analysis cited earlier reported the results of one study comparing tranylcypromine (Parnate) with placebo in patients with either bipolar I (n

Continued on Page 4

Antidepressants and Bipolar Disorder: An Update

Continued from Page 3

= 10) or bipolar II (n = 19) depression; most patients improved and there were no manic switches in either the active or placebo arms (Himmelhoch et al., *J Nerv Ment Dis* 1982;170:628-634).

More recently, a few studies have examined antidepressant monotherapy of patients specifically with bipolar II depression — intuitively, a safer therapeutic maneuver since any switch would presumably lead to a less severe hypomanic episode. Two studies have already endorsed the efficacy and safety of this approach (Amsterdam et al., *Bipol Disord* 2004;6:75-81 and Parker et al., *J Affect Disord* 2006 Jun;92:205-14), and hot off the press is another one. In this new open label study, 83 patients with bipolar II depression were randomized to receive either Effexor XR (mean dose, 186 mg/day) or lithium (mean dose, 966 mg/day). After 12 weeks, patients in the Effexor group improved more both on the Ham-D scale and on response rate (58% for Effexor vs. 20% for lithium). Only one patient in each treatment group experienced a hypomanic switch (Amsterdam and Shults, *J Clin Psychopharm* 2008;28:171-181).

The bottom line is that controlled trials are increasingly showing that antidepressants are safe and effective, either as monotherapy or as adjunctive therapy in bipolar II depression. Should we be convinced enough by these trials to treat our own bipolar II patients with antidepressants? Clinicians will have to answer that question for themselves.

Do antidepressants improve the short-term course of bipolar disorder?

Researchers break down the treatment of bipolar disorder into three phases: 1) the acute phase, lasting one to two months, and defined as treatment oriented toward treating the most dangerous and life-threatening symptoms; 2) the continuation phase, lasting 6-12 months, defined as continuing to improve symptoms until the patient is really stable, and 3) the maintenance phase, lasting one year or longer.

Most of the studies looking at antidepressants for bipolar disorder have been short-term studies, usually no longer than 10 weeks. The Gijsman meta-analysis found that patients with bipolar depression who are put on antidepressants do better over a 4 to 10 week time frame than patients put on placebo, in terms of both response rates and remission rates (*Am J Psychiatry* 2004; 161: 1537 – 1547). However, their efficacy analysis was based on only 5 studies, and 75% of patients were taking either a mood stabilizer or an atypical antipsychotic in addition to an antidepressant. Nonetheless, these results appeared to endorse the common practice of putting patients on antidepressants to pull them out of an acute depression.

But then, a large study seemed to dash these hopes. This was the Sachs study mentioned above in which 366 patients with bipolar depression (all on a mood stabilizer) were randomly assigned to adjunctive treatment with an antidepressant (either bupropion, median dose 300 mg/day or paroxetine, median dose 30 mg/day) or placebo. The primary outcome variable was "durable recovery," defined as being euthymic for 8 consecutive weeks. After 26 weeks of treatment, durable recovery was achieved in 27.3% of patients taking mood stabilizer plus placebo vs. 23.5% of patients taking mood stabilizer plus antidepressant. Basically, antidepressants added nothing of value over and above placebo (Sachs GS, et al., *NEJM* 2007;356:1711-1722).

Before you reject antidepressants in bipolar patients, though, you should know that the study's generalizability has been questioned. In an editorial accompanying the paper, Belmaker pointed out that the study initially recruited 4360 patients with bipolar disorder. Of these, 2689 patients had a depressive episode at some point and were therefore eligible to be recruited into the double blind study. But of these, only 366, or 14%, were actually enrolled (Belmaker RH, *NEJM* 2007;356:1771-1772).

While the study's authors did not report why patients chose not to be enrolled in the double blind study, we can surmise a range of typical reasons. Some may have responded well to antidepressants in the past, and didn't want to be randomized into a study where they had a 50/50 chance of getting a placebo. Others may have had poor experiences with antidepressants in the past – or at least to bupropion or paroxetine, which were the ADs used in the study. Others may have been advised by their doctors not to volunteer for other reasons. The bottom line is that the patients who actually got randomized may have particular characteristics that make them less likely to respond to antidepressants than the typical, unselected patient that you and I see in our practice. On the other hand, this argument can cut both ways, because some studies purporting to show a benefit of antidepressant treatment have generalizability problems as well.

Should we avoid maintenance antidepressants in bipolar disorder?

But what about maintenance treatment? We all have patients with bipolar disorder who improved on an antidepressant, and 5 years later, they are still taking it. Often, they will energetically resist any of our well-meaning attempts to discontinue it.

How important is it to discontinue ADs in bipolar disorder? How solid is the evidence that they make things worse over the long term?

To begin, it's pretty clear that long term studies have failed to demonstrate that keeping patients on antidepressants for years helps patients. In one study, for example, researchers located 7 blinded, controlled clinical trials in which patients were randomized to antidepressants vs. other treatments, usually lithium.

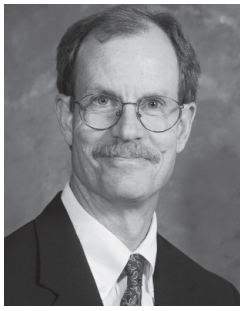
Continued on Page 8

Q&A With the Expert

The Case in Favor of the Bipolar Spectrum

Jim Phelps, M.D.

Medical Director of Corvallis Psychiatric Clinic, Oregon
Webmaster for www.psycheducation.org



Dr. Phelps has disclosed that he is on the speaker's bureau for Astra Zeneca (and has spoken about the use of Seroquel [quetiapine] in the treatment of bipolar disorder) and for GlaxoSmithKline (and has spoken about the use of Lamictal [lamotrigine] for bipolar disorder). Dr. Carlat, who conducted the interview, has reviewed the transcript to ensure a balanced presentation.

TCPR: Dr. Phelps, before we begin, I know that you have always been very up front about the fact that you speak for drug companies, and I wonder how you think this might influence what you have to say about the diagnosis of bipolar disorder?

Dr. Phelps: The bottom line is that it is very hard to know with certainty that one is not being influenced. When I give talks funded by Astra Zeneca, I wonder if I'm being perceived as a mouthpiece for the company. For example, today I'm sure we'll talk a bit about my belief that antidepressants are not appropriate for bipolar depression. I might be perceived as indirectly promoting Seroquel by discouraging people to use antidepressants. I don't see it this way — I've looked carefully at the evidence base and believe that Seroquel has some of the best evidence for the treatment of bipolar depression.

TCPR: I'm interested in your take on the idea that bipolarity lies on a spectrum. I read your recent article in the journal *Bipolar Disorders*, in which you and your colleagues at the International Society for Bipolar Disorders review the most recent evidence in support of this approach (Phelps, et al., *Bipolar Disord*.2008 Feb;10:179-93). Elsewhere in this issue, there is an interview with Mark Zimmerman about his new paper presenting a different viewpoint, namely, that bipolar disorder is sometimes overdiagnosed. Do you think that psychiatrists are overdiagnosing bipolar disorder?

Dr. Phelps: To say there is such a thing as overdiagnosis means that there is a gold standard for bipolar disorder, but that doesn't exist. The closest we have are the current DSM criteria for bipolar disorder, which are already 15 years old and there is contention about their validity.

TCPR: What is wrong with the DSM criteria?

Dr. Phelps: They are too narrow. I believe in a broader concept of bipolarity. The classic paper that I often refer to was written in 2002 by Ghaemi, Ko, and Goodwin and defined the notion of "bipolar spectrum disorder" (Ghaemi et al., Can *J Psychiatry* 2002;47:125-134). The way they did this was to focus on two characteristics that very frequently accompany bipolar disorder — family history of bipolar disorder, and hypomania in response to antidepressants — and then to survey what other characteristics are also correlated with bipolar outcome. They defined 10 variables, but I find it useful to put these variables into 5 larger categories, which have been used by Gary Sachs as the basis for what the STEP-BD calls the "Bipolarity Index."

TCPR: And what are they?

Dr. Phelps: The first is what most clinicians would consider to be the gold standard — the DSM-IV criteria for a manic or hypomanic episode. The other four are sometimes called "soft signs" of bipolar disorder. I often refer to them as "non-manic bipolar markers." They are: 1) family history, 2) early age at onset of depression, 3) course of illness, and 4) response to treatment.

TCPR: Let's start with family history of bipolar disorder. While this sounds like a pretty straightforward piece of information to attain, in practice it's not so easy.

Dr. Phelps: This is true. When you ask about family history, you have to dig for information about that relative's life and course of treatment, using the same earphones you use when listening to the patient's personal history. For example, if you hear something vague like, "Uncle John had problems and was hospitalized," you have to spend some time asking more detailed questions. What were Uncle John's behaviors? How many times was he hospitalized? What medications did he take? You might find out that Uncle John was hospitalized 5 times for mania and was given lithium and Depakote. You'd be pretty certain of a family history of bipolar disorder.

TCPR: What should we be looking for in terms of age of onset?

Continued on Page 6

Q & A With the Expert

Continued from Page 4

Dr. Phelps: The studies suggest that if the first onset of depression is between 18 and 24, these patients are more likely to have a bipolar course over time.

TCPR: And course of illness?

Dr. Phelps: This is a broad category and refers to multiple illness descriptors. The three strongest predictors are: post-partum onset of mood symptoms, the presence of psychotic features, and highly recurrent unipolar depression. Other descriptors that are less predictive are a rapid onset of depression, a relatively short duration of a depressive episode, and "atypical features" (hypersomnia, hyperphagia, leaden paralysis, rejection hypersensitivity).

TCPR: So, for example, if a patient were to present with highly recurrent depression with psychotic features, you would be quite suspicious of bipolar disorder even in the absence of a history of manic episodes.

Dr. Phelps: Right. And the final clue to bipolarity is response to treatment, which technically includes a positive response to lithium, but practically the most important is a negative response to antidepressants, particularly if that negative response includes hypomanic symptoms.

Four "Soft Signs" of Bipolar Disorder

1) Positive family history
2) Early age at onset of depression
3) Characteristic course of illness
4) Characteristic response to treatment

TCPR: Some people have proposed that patients with hypomania in response to antidepressants are in a special category, "Bipolar Disorder, type 3."

Dr. Phelps: Yes, and this reflects the results of one particularly intriguing study by Akiskal and colleagues in which they followed patients who had AD-induced hypomania over a period of time. They found that virtually 100% of these patients ended up meeting standard criteria for bipolar disorder (Akiskal et al., *J Affective Disord* 1983; 5:115-128).

TCPR: In my practice, however, it is not always easy to determine what constitutes a "hypomanic" response to an antidepressant. I often have patients reporting that they feel extremely good, even euphoric, for a brief period of time after being started on an antidepressant. That euphoria lessens over time, and then they settle into a typical antidepressant response. Should I be calling this antidepressant-induced hypomania?

Dr. Phelps: Probably not. But I have seen another variation in which mild euphoria does not diminish so quickly, lasts for two or three weeks, and when this goes away, the patient is often again depressed. I would classify that as a hypomanic response.

TCPR: The other difficulty is differentiating SSRI-induced agitation or akathisia from hypomania. When I go through a patient's past psychiatric history, it is not uncommon to hear something like, "I once took Prozac and I felt like I was crawling out of my skin. I had to stop it right away." Sometimes such patients will then report that they did fairly well on a different SSRI.

Dr. Phelps: My approach is to avoid jumping to conclusions in these cases. I'll ask, "What happened when you took Prozac," and then I'll listen with unbiased ears, as best as I can manage. If a patient says, "Oh Prozac? That was awful — my mind was flying, and I couldn't go to sleep." To me, that is beyond akathisia, and it qualifies as a hypomanic response. My criterion is an "antidepressant misadventure," as a primary care colleague put it: something that was really bad, not just jitteriness. But I won't hang my eventual diagnosis on this alone. In my subsequent interview, if I find other soft signs of bipolar disorder, I'll feel more confident that this was, indeed, an antidepressant response to be concerned about.

TCPR: To take a step back, there's clearly a great deal of disagreement in the field about how broadly we should set the standards for what constitutes bipolarity. Many would ask, "What's the point — isn't this really hairsplitting?"

Dr. Phelps: In clinical terms, the meaning of the effort to assess bipolarity is, "How willing or unwilling should I be to give this patient an antidepressant?"

TCPR: If it turned out in five or ten years that the research clearly indicated that antidepressants are safe in bipolar disorder, would there still be any reason to worry about bipolar spectrum?

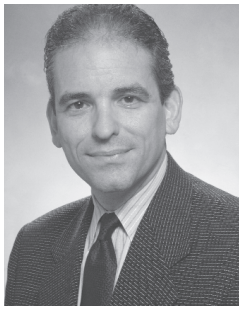
Dr. Phelps: To be frank, probably not. If there were no treatment implications, this would be an empty exercise in diagnostic semantics. In looking at the research over the years, I believe that giving patients with even soft signs of bipolar disorder an antidepressant is usually a mistake, at least in the long term. [Ed. note: For more information on the use of antidepressants in bipolar disorder, see the article "Antidepressants and Bipolar Disorder: An Update," in this issue.]

❖ ❖ ❖

Q&A With the Expert

Is Bipolar Disorder Overdiagnosed? A Conversation with Mark Zimmerman

Director of Outpatient Psychiatry,
Rhode Island Hospital
Associate Professor of Psychiatry and Human Behavior
Brown University School of Medicine



Dr. Zimmerman has disclosed that over the past 12 months he has been on the speaker's bureaus for GlaxoSmithKline (and has spoken about the use of Wellbutrin) and for Wyeth Pharmaceuticals (Effexor XR and Pristiq), and has received between $20,000 and $50,000 for these activities. He has also received research grant support from Sepracor for the study of Lunesta, and has received between $20,000 and $50,000 for this activity. Dr. Carlat has determined that these financial relationships have not commercially biased this presentation.

Many review articles on bipolar disorder in recent years begin with an introductory paragraph about the "underdiagnosis" and "undertreatment" of bipolar disorder. Indeed, it is likely that many bipolar patients are mistakenly diagnosed with major depression, because the majority of mood episodes in bipolar disorder are depressive episodes. Psychiatrists have appeared to take these warnings to heart, and may have become overly enthusiastic about the diagnosis. The first indication of this came last year, when epidemiologists at Columbia reported that bipolar disorder diagnosis in children had increased 40-fold from 1994 to 2003 (Moreno et al., *Arch Gen Psychiatry* 2007;64(9):1032-1039). Many commentators wondered if this dramatically increased prevalence reflected overdiagnosis, rather than an accurate detection of true pathology.

In June of this year, Dr. Mark Zimmerman and his colleagues published a paper indicating that overdiagnosis may be a problem in adults as well as children (Zimmerman et al., *J Clin Psychiatry* 2008;69:935-940). We caught up with Dr. Zimmerman between his projects to ask him about his research.

TCPR: Dr. Zimmerman, you recently published a paper in which you suggested that bipolar disorder is overdiagnosed in some populations. Can you describe that research?

Dr. Zimmerman: Sure. We enrolled 700 people sequentially from referrals to a community based outpatient practice in Rhode Island. These patients were fairly representative of many psychiatric practices. Most of them have medical insurance, a high percentage are female with at least a high school education, and the mean age is 39.9. We asked each of these patients whether they had ever been given the diagnosis of bipolar disorder or manic depression by a health care provider, and we found that slightly more than 20% (145 patients) had been given this diagnosis at some point.

TCPR: And then you ascertained whether or not they actually met those criteria?

Dr. Zimmerman: Yes, we gave these patients an extensive structured diagnostic interview called the SCID (Structured Clinical Interview for DSM-IV). The interview was done blind to the results of their response on the questionnaire of whether they had been previously diagnosed with bipolar disorder. And we found that fewer than half (43.4%) of the 145 patients who reported that they had been previously diagnosed bipolar were diagnosed bipolar on the SCID.

TCPR: The implication being that half of all patients who are told they have bipolar disorder do not. But did you use excessively narrow criteria in the SCID interviews?

Dr. Zimmerman: No, we asked about all four possible variations of bipolar disorder: bipolar disorder type I, bipolar disorder type II, bipolar disorder NOS (not otherwise specified), and cyclothymic disorder. We were even willing to diagnose as bipolar NOS those patients with hypomanic episodes that were shorter than the DSM-IV requirement of 4 days. So I believe we made a real attempt to capture all the patients with any version of bipolar disorder. And yet, we still found a very substantial rate of overdiagnosis.

TCPR: How do you explain your findings?

Dr. Zimmerman: Part of the difference is likely due to the possibility that some of the patients that we did not diagnose had been diagnosed in the past by clinicians using broader criteria. For example, some psychiatrists consider patients with antidepressant-induced or substance-induced hypomania to have bipolar disorder — we did not include such patients in our category of bipolar disorder NOS. [Ed. Note: According DSM-IV, antidepressant-induced or substance-induced hypomania would not be categorized as bipolar disorder NOS.]

TCPR: Assuming that you have discovered a genuine overdiagnosis problem, what are some possible reasons for this?

Dr. Zimmerman: Marketing efforts and direct-to-consumer advertising probably play a role. We have seen patients who have been urged by ads to take screening questionnaires, and then they come to their doctors wondering if they have bipolar disorder. In these cases, insufficient diagnostic rigor can lead to overdiagnosis. There are similar marketing campaigns directed toward physicians by

Continued on Page 9

Antidepressants

Continued from Page 4

More recently, the STEP-BD study group followed 1,191 patients with bipolar disorder, about 1/3 of whom were rapid cyclers (at least 4 mood episodes over the prior 12 months). They found that patients who received antidepressants over one year of follow-up were 3.8 times more likely to experience rapid cycling, and 1.7 times more likely to experience a single mood episode, than patients not receiving ADs (Schneck CD et al., *Am J Psychiatry* 2008;165:370-377).

Sounds pretty damning of antidepressants – until you realize that, since this was an observational study, we cannot know whether the antidepressants caused the cycling, or, alternatively, if the cycling caused doctors to prescribe more antidepressants. Let's face it, when a bipolar patient comes into your office profoundly depressed, it's very hard to resist prescribing an antidepressant, even when experts are warning that you might be making a bad situation worse.

The authors of the STEP-BD study interpret their findings as implying that antidepressants are "cycle-promoters," and an accompanying editorial by Nassir Ghaemi wonders if antidepressants are "mood *de*stabilizers," saying that these results "may be one more nail in the coffin of antidepressant use in bipolar disorder" (Ghaemi SN, *Am J Psychiatry* 2008;165:300-301.)

I wouldn't buy a cemetery plot yet. A study by Altshuler, published back in 2003, is still quite influential, and argues in favor of long-term AD use. In this naturalistic study, 84 patients who had a remission to an antidepressant were observed over the next year. The risk of depressive relapse among 43 subjects who stopped antidepressants within 6 months after remission was compared with the risk among 41 subjects who continued taking antidepressants beyond 6 months. Patients who discontinued had a 70% rate of depressive relapse, while those who continued had only a 36% relapse rate (Altshuler et al., *Am J Psychiatry* 2003; 160:1252-1262). But this study, like others, is flawed in various ways, including the fact that it was not a randomized clinical trial, and that the 84 patients included were selected out of an initial pool of about 1000, limiting generalizability.

So what can we say about long-term use of antidepressants in bipolar disorder? Not much. The data are sparse and of low quality. At this point, the consensus seems to be that it's best to discontinue ADs after you've stabilized your patient, but this is definitely advice in progress.

Bottom line

We've besieged you with data, and we owe you some bottom-line recommendations. Here they are:

1. Antidepressants are likely safe and effective for an acute episode of depression in bipolar disorder, particularly if the patient is already on a mood stabilizer.

2. The newer antidepressants probably are not more likely than placebo to induce manic switching, even in patients with bipolar I disorder. Tricyclics are probably more dangerous in this regard.

3. Antidepressant monotherapy (i.e., without a mood stabilizer) is probably safe and effective for patients with bipolar II depression.

4. Maintenance treatment with antidepressants may be ineffective for preventing depressive relapses, and, depending on how you interpret the studies, may actually worsen the course of bipolar disorder for patients who are rapid cyclers. So try to wean patients off these meds 6 to 12 months after remission.

5. All this advice is based on the relatively little high quality data available, so *TCPR* treatment guidelines are likely to change markedly over time, as larger studies are reported.

Research Updates IN PSYCHIATRY

ANTIDEPRESSANTS

SSRIs show weak advantage over bupropion for anxious depression

Last year, we reviewed a meta-analysis implying that bupropion is as effective as SSRIs for the treatment of patients with mixed anxiety and depression (*TCPR*, Aug 2007). In a new paper, these same researchers have sliced and diced the data a bit differently in order to answer this topic more confidently. In a pooled analysis of 10 trials, researchers found that patients with anxious depression had a higher response rate when taking an SSRI as opposed to bupropion for both depression (65.4% vs. 59.4%) and anxiety (61.5% vs. 54.5%), as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A). These differences were statistically significant. There was also a statistically significant, but very small, difference favoring SSRIs over bupropion on the mean HAM-D score. For nonanxious depression, there

Continued on Page 9

Tales from the History of Psychiatry: The History of Depakote

Valproate originally saw the light of day in the German laboratory of Beverly Burton, in 1882. She was engaged in research on fatty acids, and synthesized a new one, called 2-propylvaleric acid. But she was not able to make this acid into a salt, which is necessary in order to turn it into a solid form, and so she stopped working on it. The compound resurfaced in the 1940s when German scientists were working on creating food substitutes as part of the war effort. They succeeded in turning coal into a mixture of triglycerides that tasted a bit like butter, and they called it *ersatzbutter*. In analyzing this promising substance, they isolated the same acid that Beverly Burton had discovered in 1882. They gave it a new name, valproic acid. It turned out that it was not very useful as a nutritional supplement, however, because most of it was excreted unchanged. However, it was useful as a solvent, and it found use as a way of dissolving other drugs for research in laboratories. Fast forward to 1960, in a pharmacology laboratory at the University of Grenoble. Pierre Eymard was trying to develop a plant derivative called khelline as an antispasmodic. But he kept facing a stumbling block – khelline was very hard to dissolve. He learned about the wonderful solvent effects of valproic acid, and used it to dissolve khelline. When he injected this mixture into patients, it produced profound relaxation, leading Eymard's supervisor, Carraz, to screen valproic acid for behavioral effects. Carraz added sodium to it, creating sodium valproate, eventually doing studies of epileptics, leading to its first wide clinical use as an anticonvulsant.

In 1983, Abbott obtained a license for its use in the U.S., and came up with a new way of making the salt – by adding another sodium ion, turning it into sodium divalproate. They received a patent for this, because they successfully argued that it was easier on the stomach than valproic acid. Eventually, "Depakote" received FDA approval for the treatment of both epilepsy and bipolar disorder.

Source: David Healy, *Mania: A Short History of Bipolar Disorder*. Baltimore: The Johns Hopkins University Press, 2008.

Q & A: Is Bipolar Disorder Overdiagnosed?

Continued from Page 7

pharmaceutical companies. There has been such encouragement to avoid underrecognition that I suspect the pendulum has swung too far toward overrecognition. Finally, clinicians tend to diagnose conditions that they feel more comfortable treating. For example, if they are unsure whether a patient has bipolar disorder or borderline personality disorder they might err on the side of diagnosing a disorder that is medication responsive, as well as more likely to be covered by insurance, and perhaps less stigmatizing.

TCPR: What's the clinical significance of overdiagnosis?

Dr. Zimmerman: One is the potential for overtreatment, and the consequent overexposure to side effects of mood stabilizer treatment. Another potential problem is the degree to which some individuals, once diagnosed with bipolar disorder, cling to the diagnosis, and get very invested in it. They start looking for the "magic" pill. And in some cases, they should be more open to the idea of psychotherapy. ❖

Research Updates IN PSYCHIATRY

Continued from Page 8

were no differences in treatment outcomes between patients taking bupropion and those taking SSRIs. (Papakostas GI et al., *J Clin Psychiatry*; Published online ahead of print).

TCPR's Take: For anxious depression, this is the largest comparison between bupropion and SSRIs. The clinical relevance of the results is certainly questionable, as the average patient taking an SSRI fared less than a single point better on the HAM-D relative to the average patient taking bupropion. There were no differences between SSRI and bupropion in terms of remission rates for depression or anxiety. Based on these findings, SSRIs appear to possess, at most, a very slight advantage over bupropion for anxious depression. All trials included in the analysis were sponsored by GlaxoSmithKline, manufacturer of bupropion.

PSYCHOTHERAPY

Computer as psychotherapist?

Cognitive behavior therapy (CBT) is widely acknowledged to be the most well-researched, and possibly the most effective therapy option for a wide variety of disorders. The problem is that it is not widely available, particularly in the treatment of patients with substance abuse disorders. In this new study, researchers developed a computer-based training in CBT skills (cutely labeled CBT4CBT) specifically for the treatment of substance abuse. This program consisted of six lessons based on a CBT manual published by the National Institute on Drug Abuse. Each lesson begins with a movie illustrating a vignette in which a substance abuser fails to use appropriate skills (for example, is unable to refuse a drug when offered). This is followed by a description of the cognitive skills required and then by a repetition of the videotaped vignette in which the drug user is able to successfully use the relevant skill. Other components of each lesson include interactive assessments of symptoms, instructions on how to generalize CBT principles to situations other than substance abuse, and a videotape of a patient completing a homework assignments based on the lesson. Participants are then given the same assignment to take with them.

Continued on Page 12

CME Post-Test

To earn CME or CE credit, you must read the articles and complete the quiz below, answering at least six of the questions correctly. Mail a photocopy or fax the completed page (no cover sheet required) to **Clearview CME Institute, P.O. Box 626, Newburyport, MA 01950**; **fax (978) 499-2278**. For customer service, please call (978) 499-0583. Only the first entry will be considered for credit and must be received by Clearview CME Institute by July 30, 2009. Acknowledgment will be sent to you within six to eight weeks of participation.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the Clearview CME Institute. Clearview CME Institute is accredited by the ACCME to provide continuing medical education for physicians. Clearview CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Clearview CME Institute maintains responsibility for this program and its content.

Clearview CME Institute designates this educational activity for a maximum of two (2) AMA PRA Category 1 Credit™ or 2 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

First Name	Last Name	Degree
Street Address		
City	State	Zip
Phone	E-mail	Fax

Please identify your answer by placing a check mark or an X in the box accompanying the appropriate letter. Note: learning objectives are listed on page 1.

1. Most recent studies of manic switching have found that antidepressants added to mood stabilizers: (Learning objective #1)
- [ ] a. Rarely cause manic switching.
- [ ] b. Are associated with manic switches, but at no higher rate than placebo.
- [ ] c. Cause manic switching at three times the placebo rate.
- [ ] d. Cause switching only when the antidepressant is an MAOI.

2. Recent studies of bipolar II depression have found that: (L.O. #1)
- [ ] a. Antidepressant monotherapy is safe and effective.
- [ ] b. Antidepressant monotherapy is effective but leads to manic switching.
- [ ] c. Ethics boards will not approve antidepressant monotherapy trials.
- [ ] d. Antidepressants are effective when combined with atypical antipsychotics only.

NOTE: You must submit both pages of this special double CME test to get credit.

3. Lamictal is approved for the acute treatment of bipolar mania. (L.O. #3)
- [ ] a. True [ ] b. False

4. A possible reason for Lamictal's ineffectiveness for acute bipolar depression treatment is: (L.O. #3)
- [ ] a. It is effective at doses above 500 mg/day only.
- [ ] b. It tends to *cause* depression at low doses.
- [ ] c. It must be combined with lithium for efficacy.
- [ ] d. Its slow titration schedule prevents the achievement of an effective dose quickly.

5. According to Dr. Phelps, one study found that half of patients with anti-depressant induced mania met criteria for bipolar disorder on follow-up. (L.O. #2)
- [ ] a. True [ ] b. False

6. The study discussed by Dr. Zimmerman found that of 145 patients who had been told they had bipolar disorder: (L.O. #2)
- [ ] a. 25% met bipolar disorder criteria on the SCID.
- [ ] b. 43% met bipolar disorder criteria on the SCID.
- [ ] c. 83% met bipolar disorder criteria on the SCID.
- [ ] d. Most patients met criteria for borderline personality disorder.

7. Elements of the bipolarity index described by Dr. Phelps include: (L.O. #2)
- [ ] a. Poor response to antidepressants and decreased cycling over time.
- [ ] b. Family history, good response to antipsychotics, poor response to antidepressants.
- [ ] c. Family history, early age at onset of depression, course of illness, and response to treatment.
- [ ] d. Family history, later age at onset, and response to treatment.

8. Valproate, lithium, and gabapentin cause similar amounts of weight gain. (L.O. #4)
- [ ] a. True [ ] b. False

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

First Name Last Name Degree (M.D., Ph.D., N.P., etc.)

Your evaluation of this CME/CE activity (i.e., this issue) will help guide future planning. Please respond to the following questions:

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.

Weight Gain and Mood Stabilizers

While we have become sensitized to worrying about weight gain caused by antipsychotics, this side effect does occur with standard mood stabilizers as well. Recently, a comprehensive literature review was published evaluating the weight gain liabilities of medications commonly used to treat bipolar disorder (Torrent et al., *Acta Psychiatrica Scand* 2008;118:4-18). Here is what they found.

Lithium. Weight gain occurs in about 25% of patients, and ranges from 4.5 to 12 kg over the course of long-term treatment. Possible mechanisms: fluid retention, increased appetite, or lithium-related subclinical hypothyroidism. Polydipsia may also contribute to Li-induced weight gain, particularly if the patient drinks large quantities of high-caloric beverages.

Valproate. Weight gain occurs in 20-25% of patients, and ranges from 3-10 kg over 3-12 months, but one study reported a mean weight gain of 21 kg in 11 of 22 epileptic women over 7 years. VPA may cause polycystic ovarian syndrome in women, which may in turn contribute to weight gain.

Carbamazepine. CBZ has been shown to cause moderate weight gain in studies of epilepsy, but this has been less prominent in studies of bipolar disorder.

Looking for practical information on weight loss strategies for your patients?

The May 2005 issue of *TCPR* reviewed weight loss programs and medications, including xenical, subitramine, bupropion, and dexatrim.

You can access this issue for free at https://www.portsidetechnologies.com/thecarlatreport/documents/general/TCR_2005_05_weightloss.pdf

Gabapentin. One study of bipolar patients reported a mean weight gain of 0.9-3 kg after 12 weeks of treatment.

Lamotrigine. In many large studies, lamotrigine has been shown to produce no weight gain.

Typical antipsychotics. haloperidol, molindone, loxapine, and pimozide cause little or no weight gain in most patients.

Atypical antipsychotics.

Clozapine. Approximately 50% of patients gain at least 10-20% of body weight over several years of followup.

Olanzapine. In short-term trials, patients have gained 2-3 kg over 3-4 weeks of treatment, and about 4 kg after 10 weeks. In head-to-head comparisons, olanzapine causes more weight gain than valproate, risperidone, or ziprasidone.

Risperidone. Studies vary. One study reported a 2.5 kg gain over 3 weeks, while another showed only a 1.4 kg gain over 12 weeks.

Quetiapine. One study reported a 12 week weight gain of 2.6 kg. Another study showed no difference in weight gain between quetiapine and valproate.

Ziprasidone. Little if any weight gain.

Aripiprazole. Little if any weight gain.

Antidepressants. The following can cause significant weight gain: tricyclics, especially amitriptyline and imipramine, the MAOI phenelzine (less so tranylcypromine), paroxetine, and mirtazapine.

Research Updates IN PSYCHIATRY

Continued from Page 9

The participants were treatment-seeking outpatients recruited from a substance abuse clinic in Connecticut. Most were poly-substance abusers, with cocaine being the primary drug problem for 58%. The 77 subjects were randomly assigned to either treatment as usual (TAU – weekly individual and group therapy sessions) or TAU plus access to the CBT4CBT computer program in a small private room in the clinic. After 8 weeks of treatment, the CBT4CBT participants had a lower proportion of drug-positive urine tests (34% vs. 53%, statistically significant) and a longer number of abstinent days (22 days versus 15 days, just short of statistical significance) (Carroll KM et al., *Am J Psychiatry* 2008;165:881-888).

TCPR's Take: While the study needs to be replicated, the results are pretty impressive, indicating that simply adding a computer-based therapy to standard substance abuse treatment can yield clinically significant benefits. In an accompanying editorial (*Am J Psychiatry* 2008;165:793-795), John Greist (who discloses financial interests in computer therapies other than CBT4CBT) points out some of the inherent advantages of computer therapy, including the fact that it is always available, proceeds at the patient's own pace, is unaffected by variations in the quality of therapist training, and is much cheaper to develop and administer than either medications or human-based therapy.

The Carlat Psychiatry Report

Clearview Publishing, LLC
P.O. Box 626
Newburyport, MA 01950

PRESORTED
FIRST-CLASS MAIL
U.S.POSTAGE
PAID
MAILED FROM
ZIP CODE 37229
PERMIT 989

This Month's Focus:
Bipolar Disorder

Next Month in *The Carlat Psychiatry Report*: Treating Personality Disorders, with articles on the treatment of borderline personality disorder and an interview with Michael First, M.D.