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Long-Term Use of Mood Stabilizers in Bipolar Disorder

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Audio CD

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Long-Term Use of Mood Stabilizers in Bipolar Disorder

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Bipolar disorder is a chronic illness that often needs long-term treatment. Although data on older mood stabilizers such as lithium for the acute phase of the illness are relatively plentiful, much research remains to be done on the newer agents, such as anticonvulsants and antipsychotics, and on the long-term treatment of the disorder. In addition, practitioner awareness about the disorder and its proper treatment needs to be increased.

Rationale for the Long-Term Treatment of Bipolar Disorder

Dr. Goodwin: Without adequate treatment, bipolar disorder is chronic, relentless, and devastating. In the United States, the focus on treatment tends to be short term, perhaps because of the high mobility of our population and the fact that few clinicians have the luxury of getting to know and treat a patient for his or her whole life cycle. Just by having bipolar disorder, a person's health care costs increase immensely. Emerging evidence indicates that this gap can be reduced by effective treatment.

It is important for practitioners in psychiatry and in other medical fields to recognize that bipolar disorder is a lethal illness. The age-corrected death rate from suicide in bipolar disorder actually exceeds that in some other chronic medical illnesses.

Dr. Bowden: An important factor when considering long-term treatment of

any disease is tolerability. Tolerability drives drug selection and patient adherence; more than anything else, it determines not only effectiveness but whether a patient is going to take the drug beyond the first day, week, month, or even year of treatment.

Often, the rationale for the long-term treatment of bipolar disorder is based on the presence of subthreshold symptomatology, especially in patients with bipolar II disorder or rapid cycling. This illness rarely consists of an episode every year or so and a return to full baseline function in between episodes; some subthreshold symptoms usually remain even after the episode is resolved. It is a mistake to treat until the patient decides he or she is well and no longer needs medication. Long-term treatment drastically improves outcome for the patient with bipolar disorder.

Adverse side effects may not be the biggest reason for poor compliance. Instead, for many types of medication, poor compliance is often the result of the patients' dislike of having to take the medication; they do not like the idea of being on a maintenance medication, particularly if they feel well.

Long-Term Treatment With Lithium

Dr. Goodwin: In the 1960s and 1970s, the overall relapse rates with lithium were 34%, and without lithium, 81%. The mean duration of those studies was 20

months. In these studies, manic and depressive relapses were more effectively prevented with lithium than without.¹

Contemporary experience in lithium clinics presents a different picture than that seen in large academic studies done in the United States during the 1990s. Early controlled studies with lithium reported response rates of about 60% to 70%,^{2,3} whereas naturalistic studies report response rates of about 50%.^{4,5} For example, Page and colleagues⁴ studied 100 consecutively admitted patients, two thirds bipolar, one third unipolar. Almost half of them experienced a complete response, that is, no episodes; 41% experienced a partial response, that is, no



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hospitalizations; and 10% saw no response. Of the analyzable patients in the Maj et al.⁵ study, the overall response rate was 74%, half of which was complete response, and half was partial, that is, 50% or greater improvement. It's difficult to know all the reasons why some clinic samples are different from some academic samples.

In contrast are data from a series of academic health center studies that followed lithium-treated patients after being discharged from the hospital to determine what kind of care they received in the community. The results are discouraging: lithium was found to incon-

sistently protect against switches from depression to mania.⁶ In another study,⁷ 40% of patients experienced a manic relapse within 2 years of being discharged from the hospital.

The reasons for this decline in lithium response rates can be divided into those that reflect a changing population and those that are artifactual. Clinicians see more Axis II comorbidity and substance abuse now than previously in patients who experience an early onset of bipolar disorder. Early age at onset with more psychotic features and more substance abuse can result in poorer response to lithium. Also, more patients are exposed to antidepressants. On the artifactual side, the nature of studies of lithium has changed. The early studies were conducted in populations that had never been exposed to the drug by researchers skilled in lithium use. More recent studies suffer from a selection bias, that is, the patients tend to be those who have not been responsive to existing treatments, especially lithium.

Whether lithium loses its effectiveness in some patients over time is an issue that has not been definitively settled. The major studies of maintenance lithium treatment in manic depressive illness have a variety of methodologies with about 3000 patients and about 23,000 patient years. A review⁸ of these studies showed that 78% of the patients had bipolar disorder, and the remainder had a recurrent unipolar disorder. The recurrence risk with lithium treatment is lower in all studies, and overall there was a 3.2-fold reduction in recurrence risk and an 80% reduction in hospitalization. In the placebo-controlled parallel-group studies, the recurrence risk was 3.6-fold lower with lithium. No difference in the

mean reduction of recurrence risk was found in those trials that involved prior lithium withdrawal as opposed to those that did not.

Other studies have compared patients with rapid cycling and those without rapid cycling and found lithium to be superior to anticonvulsants. Also, among the non-rapid-cycling patients, there was a trend for both lithium and divalproex to be superior to carbamazepine among patients with rapid cycling.

Important issues such as whether or not lithium can help rapid cyclers and the effect of lithium in the absence of antidepressants were studied by Kukopulos and coworkers.⁹ They followed a group of 50 patients with rapid cycling for over 1 year, most of whom were also taking an antidepressant. Only 8 patients (16%) responded to lithium treatment, a rate similar to that in other studies. But when 21 of these 50 patients discontinued their antidepressant, 15 (71%) then stabilized on lithium treatment.

Bowden and coworkers¹⁰ conducted a 1-year head-to-head comparison of lithium, divalproex, and placebo in the pro-

phylactic treatment of bipolar disorder. The 2 active ingredients had similar efficacy on the primary outcome measure, time to recurrence of a mood episode. In terms of difficulty using these 2 drugs, there are systems and drug interactions that need to be monitored in both cases. Lithium has the advantage in preventing suicide; divalproex hasn't been in use long enough to collect that kind of data. The review⁸ found 7- to 8-fold reduction in suicides with lithium treatment. Preventing suicide is of utmost importance in the treatment of bipolar disorder since, as physicians, one of our main responsibilities is saving lives.

A recent placebo-controlled study of the prevention of mania and depression compared lithium with lamotrigine.¹¹ Lithium separated from placebo in time to intervention for a manic episode, whereas lamotrigine did not. On the other hand, with time to intervention for depression, only lamotrigine separated from placebo—lithium did not.

Dr. Calabrese: The data suggest that lithium's antimanic properties exceed its antidepressant properties.

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© *Preventing suicide is of utmost importance in the treatment of bipolar disorder since, as physicians, one of our main responsibilities is saving lives.*

Dr. Goodwin: There are 3 different types of lithium literature and how one is interpreted in light of the others can be complicated. There is the old lithium literature from the 1960s and 1970s that has few dropouts, and there are 2 contemporary lithium literatures—U.S. literature and that of the rest of the world—which are different from one another. For example, we have much more substance abuse in the United States. Antidepressants are used to treat bipolar disorder more often. Many studies in the United States do not follow dropouts, so the biggest problem with U.S. longitudinal data is how to analyze data with such a high dropout rate.

Long-Term Treatment With Anticonvulsants

Carbamazepine

Dr. Keck: In contrast to the large number of studies regarding lithium, there are fewer studies with carbamazepine in the long-term treatment of bipolar disorder. An enormous number of limitations exist in the way the carbamazepine studies were conducted, so we still lack conclusive evidence of

carbamazepine's efficacy as a long-term treatment. However, there are many indicators that it is successful for some patients.

In 1995, Dardennes and colleagues¹² looked at the 4 existing studies of carbamazepine maintenance treatment. In 3 of these 4 studies, carbamazepine appeared to be comparable to lithium in that there were no statistically significant differences in efficacy. However, most of these studies had insufficient sample sizes. One study, which was also underpowered, nevertheless found that lithium was more effective than carbamazepine in prevention of relapse. These early studies suggested that carbamazepine might be as effective as lithium, but they were not designed to give conclusive answers.

A more recent study by Greil and colleagues^{13,14} was an open-label, randomized study that compared carbamazepine with lithium for 2½ years. The study included 144 patients. No drug or alcohol abuse was allowed, so results may not be easily generalized to a broader population of bipolar disorder patients, among whom substance abuse is rather common. The outcome measures were the rate of hospitalization, rate of overall recurrence, rate of concomitant medications, and rate of dropout due to recurrence and/or need for concomitant medications and/or severe side effects.

The average lithium level in this trial^{13,14} was only 0.6 mmol/L, and the average carbamazepine dose was only 621 mg/day, both of which are in the lower end of the recommended therapeutic range in the United States. Concomitant medications were allowed for breakthrough symptoms and recurrences.

No significant differences were reported in the rate of hospitalization.

between the lithium and carbamazepine groups, although a numerically greater percentage of carbamazepine-treated patients required hospitalization compared with lithium-treated patients.¹⁴ There was also a trend for a greater risk of recurrence overall with carbamazepine compared with lithium. Significantly greater efficacy of lithium over carbamazepine was demonstrated when outcome was assessed as the need for concomitant medication, which implies the presence of subsyndromal symptoms that need medication but that might not meet criteria for full-blown recurrence of an episode. There was a significant difference in relapse rate—67% for carbamazepine compared with 44% for lithium.¹⁴ If tolerability and dropout because of adverse side effects are included, we see an even greater difference with 71% of patients having recurrence, need for other medications, or dropping out because of adverse events in the carbamazepine group compared with 46% in the lithium group.¹⁴

A second study with only 52 patients by Denicoff and coworkers¹⁵ was a 3-year study of a different design. Rather than the parallel-group design of the Greil et al.^{13,14} trial, this was a crossover study in which patients received lithium or carbamazepine for the first year of treatment, were switched over to the alternative agent in the second year of treatment, and then received combination treatment in the last year of treatment. Augmentation or rescue medications were allowed.

The Denicoff et al. study¹⁵ found no significant differences in time ill between patients who received lithium versus those who received carbamazepine. This study is one of the few to have enough data in a combination group versus a

monotherapy group to suggest better efficacy for combination therapy. Combination therapy is a remarkably understudied topic in the long-term treatment of bipolar illness, and it is even more remarkable when we realize that many, if not most, patients in the United States are on combination therapy. These data need to be taken in the light of the extensive need for adjunctive treatment in the study. Among lithium-treated patients, 45% required rescue or addition of an antidepressant drug for breakthrough depressive symptoms. A similar number in the carbamazepine group and a similar number in the combination group required such treatment. Need for comedication was not considered treatment failure in this study.



Combination therapy is a remarkably understudied topic in the long-term treatment of bipolar illness.

Valproate

Dr. Keck: For valproate, even fewer long-term studies have been conducted, but they provide somewhat greater evidence of efficacy, especially in patients who begin taking valproate for acute treatment and then stay on long-term valproate treatment. An 18-month trial by Lambert and Venaud¹⁶ compared the valpromide formulation of valproate, which is available in some European countries, with lithium. This study found trends in favor of the valpromide group to

have a lower number of overall mood episodes averaged, but these differences were not statistically significant. These data are the first available from a controlled trial that suggest that valproate might be as effective as lithium as maintenance therapy.

Of course, the most rigorous study on this point was the 1-year randomized study¹⁰ in which patients received either divalproex, lithium, or placebo in a parallel-group, double-blind manner. This study was designed such that patients received medication as needed during an open-label treatment period and then received divalproex or lithium only at the end of the open-label period. It had the advantage of aiming for maintenance therapeutic levels of each comparative agent. The primary endpoint was time to recurrence of a manic episode defined as hospitalization for mania or a Mania Rating Scale (MRS) score greater than 16.

The overall results of this study¹⁰ were most notable for those patients who started on divalproex treatment and continued with divalproex or were randomly assigned to placebo. There was a significant difference in favor of divalproex over placebo in the number of patients who stayed in the maintenance phase of the study. There was also a trend for patients in the divalproex group to have a lower rate of termination from the study for mania or depression, but no significant difference in termination for intolerance or noncompliance. The number of patients completing treatment who started with divalproex and continued with divalproex was significantly higher compared with patients who started on divalproex treatment and then were randomly assigned placebo or lithium. The

patients who received divalproex took the drug for 200 days on average compared with about 143 days for patients switched to placebo and 162 days for the patients switched to lithium.

In another study,¹⁷ patients were initially enrolled in a study of valproate or lithium monotherapy plus placebo versus olanzapine plus lithium or valproate for breakthrough manic or hypomanic symptoms. A significant difference was noted in favor of the combination therapy—olanzapine plus lithium or olanzapine plus valproate—in preventing overall relapse compared with lithium or valproate alone. The difference is even more robust for prevention of recurrence into a manic episode in the combination group.

Dr. Suppes: In my experience with our study¹⁸ on optimizing treatment, all patients received combination therapy. I was surprised at how few complaints of side effects I heard.

Dr. Goodwin: We have too little combination data that is controlled. The Stanley Foundation¹⁹ reports that three fourths of patients with bipolar disorder are taking 2 or more medications, and 25% of them are taking 4 or more. A huge gap exists between what people need to know in clinical practice and what they can find out from existing large, controlled studies.

Lamotrigine

Dr. Calabrese: A large international team of investigators from 15 countries and I have conducted several placebo-controlled studies of lamotrigine in bipolar disorder.^{20–22} Study 602²⁰ compared placebo with 50 and 200 mg/day of lamotrigine in 195 patients with bipolar depression. It is, to my knowledge, the first placebo-controlled, monotherapy, bipolar

I depression study. Patients taking the 200-mg/day dose of lamotrigine began to improve by week 3, and both doses were more effective than placebo.



A huge gap exists between what people need to know in clinical practice and what they can find out from existing large, controlled studies.

Study 602 lasted only 7 weeks, whereas Study 606²² included an 18-month follow-up period. Study 606 was conducted in 349 bipolar I outpatients who were given 100–400 mg/day of lamotrigine in an open-label fashion for up to 16 weeks. Of these, 175 stabilized and were randomly assigned to lamotrigine, lithium, or placebo and were followed for 18 months. Patients were recently manic and did not have to have a history of response to lithium to get into this study. Randomization criteria included 4 consecutive weeks of a Clinical Global Impressions-Severity scale (CGI-S) score of mild or lower during the open-label lamotrigine monotherapy period, lamotrigine therapy lasting for a minimum of 8 to 16 weeks, and discontinuation of other medications without relapse.

The primary outcome measures included time to additional pharmacotherapy for symptoms of a mood episode or emerging symptoms of a mood episode.²² Secondary outcome measures

included overall survival with time to dropout or time to intervention for emerging symptoms of mania, hypomania, or mixed states; time to intervention for depression; and changes in the symptom-severity scales (the MRS and the Hamilton Rating Scale for Depression [HAM-D]) and the global measures (the CGI-S, CGI-Improvement [CGI-I], and Global Assessment Scale [GAS]). The median time to dropout was 8 weeks for the placebo group, 12 weeks for the lamotrigine group, and 14 weeks for the lithium group.

Dr. Goodwin: Does this include dropouts for side effects?

Dr. Calabrese: This includes dropouts for all reasons.²² The existing lithium literature does not include survival analysis such as this; if it did, it might tell a different story.

Premature terminations by type were for mania, 40% of placebo patients, 17% of lithium patients, and 34% of lamotrigine patients; for depression, 30% of placebo patients, 22% of lithium patients, and 14% of lamotrigine patients.²² Dropout rates due to adverse events were 4% of placebo patients, 24% of lithium patients, and 5% of lamotrigine patients. Side effects primarily included nausea and diarrhea.

A rash study²³ put together all the rash rates—both benign and serious—in both placebo-controlled and open-label mood disorder trials with lamotrigine. The total number of exposures is now 3153. The benign rash rate on lamotrigine was 12%. There were 2 serious rashes defined by both discontinuation and hospitalization, generating a serious rash rate of less than 1%. In the placebo-controlled studies, 1198 patients were treated with lamotrigine, and a 9% rash rate was reported.

Ketter and I²⁴ have also examined stabilization of mood from below versus above baseline. Lamotrigine can be described as a prototype of a class B mood stabilizer—a mood stabilizer that has antidepressant effects without causing switching or episode acceleration—whereas the other mood stabilizers are class A mood stabilizers that have anti-manic effects without causing a worsening of depression. Therefore, no mood stabilizer possesses a great degree of efficacy in both phases of the illness. There is an emerging consensus that mood stabilization is often achieved through the use of agents that possess complementary efficacy.

The literature suggests that in the acute management of mania, we should start with divalproex, lithium, carbamazepine, or atypical antipsychotics and then move quickly to lamotrigine augmentation. In the management of depression—be it bipolar I or bipolar II—we should start with lamotrigine and then move quickly to augmentation with a type A mood stabilizer as soon as patients begin to cycle into a high.

One could argue that in patients with bipolar II rapid cycling, the lamotrigine data are positive in hypomania. For the most part, I would recommend starting as proposed, move quickly to augmentation, and avoid antidepressants in bipolar depression, if at all possible.

Dr. Keck: A study comparing the combination of lithium and lamotrigine versus the combination of lithium and an antidepressant could help determine if lamotrigine has antidepressant effects without causing a switch to mania.

Dr. Goodwin: The Quitkin et al.²⁵ study had a 2½-year random assignment to lithium alone versus lithium plus imipra-

mine. They saw absolutely no advantage for the combined treatment in the prevention of depression. It was 10% in one cell and 8% in the other. On the other hand, they saw a 2½-fold increase in manic switches in the combined treatment group.



Mood stabilization is often achieved through the use of agents that possess complementary efficacy.

Long-Term Treatment With Antidepressants

Dr. Kusumakar: The use of antidepressants in bipolar disorder is a topic of great interest because antidepressants are among the most commonly used medications in bipolar disorder, most likely because depression is a common type of episode. If a patient has depression, good predictors of future bipolarity are psychotic symptoms present as a part of depression; a family history of bipolar disorder, particularly in first-generation relatives; or pharmacologically induced hypomania or mania. Other possible predictors include a young age at onset of depression, reverse vegetative symptoms, psychomotor retardation, agitated depression, and episodicity.

When treating depression in bipolar disorder, there are 3 critical questions to ask: Is the treatment efficacious? Does the antidepressant treatment maintain euthymia or does it induce switching to mania or hypomania? Does the treatment alter the cycle frequency? Many studies

report high rates of antidepressant-induced manic episodes. The reported switch rates vary widely, and tricyclic antidepressants are the most common offenders. In a study of bupropion and desipramine, Sachs and colleagues²⁶ showed clearly that desipramine produces a switch to mania much more commonly than bupropion over a 12-month period. The question of whether antidepressants induce rapid cycling has not been fully established, since long-term studies are few and far between.



Many studies report high rates of antidepressant-induced manic episodes.

Dr. Goodwin: The problem with short-term studies of switching may be false negatives, simply because there is not enough time to pick up switches. The Quitkin et al.²⁵ study is a long-term study that found that antidepressant treatment in combination with lithium was associated with 2½ times more manic switches with no more protection against depressive episodes compared with lithium alone.

Dr. Calabrese: Antidepressants can have negative effects on the clinical course of bipolar illness.

Long-Term Treatment With Antipsychotics

Dr. Kusumakar: The use of antipsychotic drugs in bipolar disorder is also common. A high number of patients who enter an inpatient unit with mania may continue on an antipsychotic medica-

tion, not only at discharge but many months later as well. Antipsychotics as a class, irrespective of whether they are conventional or atypical, have very clear antimanic effects.

Most clinicians know that extrapyramidal symptoms and dystonia are commonly associated with the conventional antipsychotics. Some evidence suggests that tardive dyskinesia is significantly increased in patients with mood disorders compared with patients with schizophrenia. One would not recommend conventional antipsychotics for long-term use in bipolar disorder. However, the atypical antipsychotics have some antidepressant effects. In prophylaxis, a follow-up with olanzapine from an acute mania study demonstrated that Young Mania Rating Scale (YMRS) scores decreased and stayed down for over a year.²⁷ Patients in this open phase could receive other medications, so it was not olanzapine monotherapy, but certainly encouraging. Depressive symptoms also decreased and stayed down, although many patients received fluoxetine in addition to olanzapine.

Vieta and colleagues²⁸ treated over 540 patients with risperidone added on to a variety of other medications; the sample is characterized well in terms of diagnosis but not in terms of what concomitant treatment they received. Be that as it may, these patients' YMRS scores and depressive symptoms decreased. Certainly, risperidone and olanzapine are not associated with exacerbation of mood symptoms, and olanzapine has low propensity for tardive dyskinesia.

Weight gain is of great concern with antipsychotic treatment. The data from the Allison et al.²⁹ analysis can be divided into 3 groups: clozapine, olanzapine, and

thioridazine were associated with the greatest weight gain. The middle group included risperidone, and a lower group included ziprasidone. The data are not conclusive about quetiapine. Weight gain increases the risk for diabetes and other cardiovascular conditions. When prescribing atypical antipsychotics, the clinician must inquire about the patient's family history of obesity, diabetes, and cardiovascular disease; take baseline measurements of body mass index and lipid, triglyceride, and fasting blood glucose levels; and conduct a baseline electrocardiogram if indicated. These measurements should be repeated during treatment with atypical antipsychotics.

Dr. Suppes: An interesting question is how these medications should be used in the overall treatment of patients with bipolar disorder. There's still a relative paucity of studies in the long-term use of these drugs.

Dr. Calabrese: How is it possible that there is so much positive data with regard to antipsychotics and still so much unmet need? They work in mania, they work in mixed states, they work in psychosis. Study results do not always translate into clinical results that we see in our patients.

Dr. Goodwin: Selection factors clean up samples before they get into the highly controlled studies, so study samples do not reflect the population that you face in the office.

Dr. Kusumakar: My group has been involved in an atypical antipsychotic maintenance study, and to recruit 5 patients into the study, we had to screen 73 patients, suggesting that the patients who went into this study were a very select group.

In some ways, that is one of the difficulties about any study, regardless of the medication being studied, because clinicians recognize that the sample is not what they see in the office.

Long-Term Treatment of Bipolar II Disorder

Dr. Suppes: Many of the studies we have discussed thus far were conducted in patients with bipolar I disorder. However, bipolar II disorder, characterized by major depressive episodes and at least one hypomanic episode, also presents a diagnostic and treatment challenge. There's a fair amount of underdiagnosis of the illness, but many data support that it is a distinct and separate illness from bipolar I disorder. A conservative estimate for the prevalence of bipolar II is around 0.5%,³⁰ which translates to about 2 million people with bipolar II disorder in the United States.

The course of illness and psychosocial disability associated with the disorder are at least as severe if not more so as that reported with bipolar I disorder. Some studies report more frequent mood episodes, particularly depression, than with bipolar I, and some report a similar frequency of episodes. Suicide is an imperative issue for bipolar disorder in general. Bipolar II disorder is associated with a higher suicide risk than bipolar I disorder; studies have reported a higher number of completed suicides with bipolar II.³¹ A high rate of comorbidity has also been reported.³²

As in bipolar I disorder, though, lithium remains the first-line treatment for bipolar II disorder. The corrected study by Dunner and coworkers^{33,34} showed that lithium was more effective

than placebo for depression in bipolar II disorder. Although there was an advantage of lithium over placebo numerically for mania, the difference was not significant. The Greil et al. study^{13,14} included patients with bipolar II disorder and bipolar disorder not otherwise specified. Lithium was found to be about as effective as carbamazepine.

Dr. Keck: In a derivative analysis³⁵ of Greil¹⁴ of 57 patients with bipolar II disorder or bipolar disorder not otherwise specified, the same outcome measures were assessed as in the entire group. There were no significant differences overall in those outcome measures.

Dr. Suppes: Amsterdam and colleagues^{36–38} did 3 post hoc studies on major depression, and data on patients with bipolar II disorder were analyzed retrospectively and compared with a matching unipolar control group. Patients with bipolar II disorder responded to fluoxetine monotherapy.³⁶ The more extended survival analysis, however, showed a limited survival range. The overall, long-term survival rate was relatively low for the group with bipolar II disorder. The authors emphasized how low the manic switch rate was, but 20% of the bipolar II sample reported agitation.³⁶ The authors were not looking for hypomania, so they did not necessarily recognize agitation as a symptom of hypomania.

This study³⁶ raises the question, what is the first appropriate step for treating bipolar II disorder? Trials directly addressing appropriate treatment for bipolar II disorder are needed.

A study by Winsberg and colleagues³⁹ examined the response to divalproex in medication-naïve patients versus mood stabilizer-naïve patients. *Medication-naïve* means that the patient has never

taken medication of any class for bipolar II disorder. *Mood stabilizer-naïve* implies that the patient may have been treated with a medication other than a mood stabilizer, such as an antidepressant. Medication-naïve patients experienced a greater improvement in depression compared with mood stabilizer-naïve patients as measured by the HAM-D.

A study by Calabrese and coworkers²¹ examined the effect of lamotrigine on rapid cycling. As in Study 606,²² patients were given lamotrigine in an open-label fashion until stabilized and were then randomly assigned to monotherapy with lamotrigine or placebo for 6 months. Of the patients included in the 6-month randomized phase, 52 had bipolar II disorder. Median time to pharmacologic intervention was 17 weeks in the lamotrigine group and 7 weeks in the placebo group. At study endpoint, 46% of the bipolar II patients who received lamotrigine were still stable compared with 18% of the patients who received placebo, significant at $p < .05$; the difference was not significant between treatment groups in the bipolar I population. In terms of effectiveness, overall clinical utility, and time to dropout for any reason, the study is positive overall, but the positive results are clearly carried by the bipolar II population.

Dr. Bowden: Bipolar II disorder may have a very different illness course than bipolar I disorder.

Dr. Suppes: True, so if a treatment is effective for bipolar I disorder, is it good for bipolar II? Different treatments may be needed.

Dr. Bowden: Rapid cycling is highly associated with bipolar II disorder and vice versa. By definition, bipolar II disorder is characterized by full depressive episodes, so it is unsurprising that depressive as-

pects of bipolar II disorder are likely to first lead the clinician to misdiagnosis and mistreatment. The implication is that the strategies in terms of first-line and second-line treatments are not going to be the same for bipolar I disorder and bipolar II disorder or for mania-dominant forms of bipolar disorder compared with depression-dominant forms.

Dr. Goodwin: Should we think of bipolar II rapid cyclers like we think of bipolar I rapid cyclers in that this is a difficult form of the illness that needs combined therapy, or would this data²¹ support lamotrigine monotherapy for patients with bipolar II and rapid cycling?

Dr. Suppes: It is too soon to tell.

Dr. Keck: What about bipolar II patients who do not have rapid cycling but who are depressed. Do you use lithium? Do you use an antidepressant alone? Do you use lamotrigine alone?

Dr. Suppes: I don't think this has been resolved. In my own practice, I've got bipolar II patients taking lamotrigine alone. Some take antidepressants alone because they did not respond to anything else or were intolerant of other medications.



It is unsurprising that depressive aspects of bipolar II disorder are likely to first lead the clinician to misdiagnosis and mistreatment.

Conclusion

Dr. Bowden: Bipolar disorder remains a challenging disorder to diagnose and treat. The standard mood stabilizers are difficult to use and require constant monitoring, although they are effective for many patients. Novel treatments from a variety of drug classes, including anti-convulsants, antidepressants, and anti-psychotics, may prove to be effective for bipolar disorder without the challenges of the older mood stabilizers. More work remains on defining treatments for bipolar disorder and on discovering if medications effective for one type of the disorder will be effective in other types as well.

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Drug Names: bupropion (*Wellbutrin and others*), carbamazepine (*Carbatrol, Tegretol, and others*), clozapine (*Clozaril and others*), desipramine (*Norpramin and others*), divalproex (*Depakote*), fluoxetine (*Prozac and others*), imipramine (*Surmontil, Tofranil, and others*), lamotrigine (*Lamictal*), olanzapine (*Zyprexa*), quetiapine (*Seroquel*), risperidone (*Risperdal*), thioridazine (*Mellaril and others*), ziprasidone (*Geodon*).

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*J Clin Psychiatry Audiograph Vol. 5 No. 6 July 2002
Long-Term Use of Mood Stabilizers in Bipolar Disorder*

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1. The rationale for the long-term treatment of bipolar disorder is based on:
 - a. The pattern of minor episodes every year or so with a return to full functioning between episodes
 - b. The presence of subthreshold symptomatology
 - c. The high mobility of the U.S. general population
 - d. None of the above; bipolar disorder never warrants long-term treatment
2. In bipolar disorder, adverse side effects are the main reason for noncompliance with medication.
 - a. True
 - b. False
3. The reasons for the apparent decline in the efficacy of lithium in the United States can be attributed to:
 - a. Changes in the U.S. population
 - b. Changes in the diagnostic criteria
 - c. Changes in the way studies are conducted
 - d. All of the above
4. What is the problem with data on combination therapy in bipolar disorder?
 - a. None; the data are clear and helpful.
 - b. Combination therapy has been poorly studied; the data are inconclusive and untrustworthy.
 - c. Combination therapy is understudied; data are lacking.
 - d. Combination therapy has been overstudied; there are too many data to be helpful.
5. Mood stabilization is often achieved through the use of:
 - a. A single, effective agent
 - b. Agents that possess complementary efficacy
 - c. A "wait-and-see" approach before pharmacotherapy is initiated
 - d. Several short trials of different agents
6. Which of the following is *not* one of the 3 critical questions to ask when treating bipolar depression?
 - a. Is the treatment efficacious in treating depression?
 - b. Does the treatment induce switching to mania or hypomania?
 - c. Is the treatment efficacious in treating psychosis?
 - d. Does the treatment alter cycle frequency?
7. A conservative estimate for the prevalence of bipolar II disorder in the United States is:
 - a. 0.5%
 - b. 1%
 - c. 5%
 - d. 10%

CME REGISTRATION FORM

*J Clin Psychiatry Audiograph Vol. 5 No. 6 July 2002
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Circle the one correct answer for each question.

1. a b c d 5. a b c d
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