Mood State at Study Entry as Predictor of the Polarity of Relapse in Bipolar Disorder

Joseph R. Calabrese, Eduard Vieta, Rif El-Mallakh, Robert L. Findling, Eric A. Youngstrom, Omar Elhaj, Prashant Gajwani, and Ronald Pies

Of the placebo-controlled maintenance studies conducted in bipolar disorder, few have enrolled patients who present depressed. In fact, only lithium and lamotrigine have been studied over the long term with placebo-controlled designs in recently manic and recently depressed bipolar patients. Given the magnitude of the unmet medical need and the data suggesting that symptomatic patients with bipolar disorder spend the majority of their time depressed, this is unfortunate. Our review of the pre-lithium literature and more recent publications suggests that mood state at study entry predicts the polarity of relapse and the response to treatment. Accordingly, a need exists to enroll recently depressed patients in maintenance studies to elucidate the complete spectrum of efficacy of putative mood stabilizers and improve the long-term treatment of bipolar depression. Patients presenting depressed for a maintenance study tend to relapse into depression; those presenting manic, into hypomania/mania/mixed states. This is particularly true during the first several months of the randomized treatment. The polarity of the index episode tends to predict the polarity of relapse into a subsequent episode in a ratio of about 2:1 to 3:1. We conclude that putative mood stabilizers must be tested in recently manic and recently depressed patients to determine their spectrum of prophylactic efficacy.

Key Words: Index episode, bipolar, relapse, predictor, mania, depression

Recent research on bipolar disorder (BPD) has highlighted the pervasive and debilitating nature of bipolar depression. For example, evidence from the National Institute of Mental Health (NIMH) Clinical Collaborative Study suggests that of time spent symptomatic, patients with bipolar I disorder experience depressive symptomatology approximately three times as frequently as hypomanic or manic symptoms (Judd et al 2002). This disparity increases dramatically in bipolar II disorder (Judd et al 2003). And yet, although the depressive symptoms of BPD are associated with high morbidity, mortality, and overall burden (Goodwin and Jamison 1990; Judd et al 2002), few randomized, controlled studies have enrolled patients from this phase of the illness. Indeed, there seems to be a disparity between the phase of the illness that has the most unmet medical need and the type of patients historically enrolled in maintenance studies. Whereas most patients with bipolar disorder spend more time depressed than manic, most maintenance studies have enrolled patients who were currently or recently manic (Bowden et al 2003; Calabrese et al 2003).

There is evidence from both the pre-lithium era and more recent published studies suggesting that the patient's index episode (mood state at study entry) has both therapeutic and prognostic implications (Quitkin et al 1986; Shapiro et al 1989). Shapiro describes the "index episode" as being "the episode that brought the patient into a particular study" (Shapiro et al 1989), usually as a consequence of hospitalization or admission to an outpatient clinic. The index episode might or might not be the patient's first affective episode. When Shapiro et al observed an interaction between type of index episode and treatment outcome, they recommended that patients be stratified in subsequent maintenance therapy trials according to type of index episode—manic or depressive—and then be randomized to treatment groups separately. Despite these early recommendations, this methodology has only rarely been used. The only medications that have been evaluated in similarly designed placebo-controlled maintenance studies in both the recently manic and recently depressed have been lithium and lamotrigine (Prien et al 1973a, 1973b, 1974, 1984; Bowden et al 2003; Calabrese et al 2003).

In this review, we examine the hypothesis that "mania begets mania, and depression begets depression" and explore the implications for the design of future bipolar maintenance studies. Though the relationship between index episode and significant improvement in treatment outcome is an important area of research, it will not be the primary focus of this review. Rather, we will focus on the natural history of BPD, as elucidated through long-term studies that have randomized patients to placebo. Owing to the diverse maintenance study methodologies used, formal meta-analyses are not feasible. After a historical review, this article focuses on the published placebo-controlled maintenance studies using random assignment to parallel treatment arms that provide data regarding the polarity of the index episode and subsequent mood episode (e.g., upon rehospitalization or drug intervention). There is also a diverse naturalistic literature that informs various aspects of the hypothesis under question, and an attempt has been made to focus on publications of strategic importance. Owing to the complexity of maintenance methodology and the need for detailed information regarding study designs, only published maintenance data will be reviewed. Because of limitations of space and literature, this review will not address the extent to which minor or subclinical depressive or hypomanic states predict the polarity of relapse.

We will conclude that the available evidence suggests that the polarity of the index episode has important implications for the development of mood stabilizers. Before an agent's spectrum of mood-stabilizing properties can be fully understood or generalized, studies involving both manic and depressive index episodes must be conducted, either through separate studies or a properly powered study that stratifies for the index episode.

From the Case University School of Medicine (JRC, RLF, EAY, OE, PG), University Hospitals of Cleveland, Cleveland, Ohio; Bipolar Disorders Program (EV), Clinical Institute of Psychiatry, University of Barcelona, Barcelona, Spain; Department of Psychiatry and Behavioral Science (RE-M), University of Louisville, Louisville, Kentucky; and the Tufts University School of Medicine (RP), Boston, Massachusetts.

Address reprint requests to Joseph R. Calabrese, M.D., University Hospitals of Cleveland, 11400 Euclid Avenue, Suite #200, Cleveland, OH 44106; E-mail: joseph.calabrese@uhhs.com.

Received March 8, 2004; revised August 5, 2004; accepted September 21, 2004.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2004.09.022

Historical Context

In 1986, Quitkin et al (1986) first asked the question, "Are there manic-prone and depressive-prone forms ... [of BPD]"? Evidence from the pre-lithium era studies (Lundquist 1945; Perris 1968) suggested that if the patient's first episode was manic, there was increased risk of manic (vs. depressive) relapse. For example, in the Lundquist data (Lundquist 1945) as analyzed by Quitkin et al (1986), 43 of 95 patients who recovered from a first episode of mania had a second episode of the illness. (The relatively low recurrence rate during the observation period [10–30 years] was probably due to the fact that only episodes requiring hospitalization were included.) Of the 43 second episodes, 32 were manic (74%), and only 5 were depressive (12%). Similarly, in an observation period of 18–20 years, Perris (1968) found that the first episode was manic in 39 of 131 bipolar patients; of these, 24 (62%) had more frequent manic than depressive episodes. Conversely, in the 67 patients whose illness began with a depressive episode, 59 (88%) had mainly depressive episodes. Interestingly, Morgan (1972) found that in 29% of patients (12 of 41), depressive symptoms followed an index episode of hypomania. In six cases, depressive symptoms were judged sufficiently severe to warrant somatic treatment. However, data were retrospective and collected only up to 3 months after discharge from the hospital; moreover, manic/hypomanic symptoms were apparently not investigated (Morgan 1972).

A review by Quitkin et al (1986) of pre-lithium era data and of six controlled studies of lithium between 1970 and 1981 (Baastrup et al 1970; Cundall et al 1972; Prien et al 1973a, 1973b; Quitkin et al 1981; Stallone et al 1973) suggested that the polarity of the index episode seems to be correlated with the polarity of the following episode. Specifically, Quitkin et al (1986) concluded that 1) there is some support from the pre-lithium era data for the hypothesis that patients whose first episode is manic are more likely to have increased risk of manic relapse; and that 2) there might be a relationship, according to data from the lithium era, between the type of index episode and future episodes, whether the patient is taking placebo or the drug (Quitkin et al 1986).

Published, placebo-controlled trials of long-term treatment are summarized in Table 1, based on Goodwin and Jamison's original analysis (Goodwin and Jamison 1990) and that of Quitkin et al (1986). It is appropriate to comment in some detail on the Prien et al studies, because, unlike most, these were similarly designed "companion" studies, involving patients in both phases of the illness. In the first of these studies (Prien et al 1973a), patients ($N = 205$) were recruited at the time of discharge from the hospital, after treatment of acute mania. Patients were randomly assigned to lithium carbonate ($n = 101$) or placebo ($n = 104$). Those assigned to lithium continued at the established maintenance level; those assigned to placebo had identically appearing placebo capsules substituted for lithium. The treatment physician knew the identity of the patient's medication, whereas clinical raters and patients were blinded. Patients returned to the hospital every 4 weeks to be rated, obtain medication, and have their serum lithium levels monitored (to maintain levels of .5–1.4 mEq/L). A patient was considered "relapsed" if he or she had a manic or depressive attack requiring hospitalization or supplementary drugs (i.e., medications other than the patient's assigned treatment). Several assessment scales were used, including the Global Affective Scale, which was completed by the treating physician at 4-week intervals. Outcome in the placebo group showed a striking preponderance of manic episodes (71 of 104, or 68%) versus depressive episodes (27 of 104, or 26%). The difference between the placebo and lithium groups was due mainly to the higher incidence of manic episodes in the placebo group. However, both groups showed a predominance of manic over depressive relapses.

In the second of the two controlled "companion" studies, Prien et al (1973b) examined bipolar I patients ($n = 44$) with a depressive index episode. Newly remitted patients were randomly assigned to lithium ($n = 18$), imipramine ($n = 13$), or placebo ($n = 13$). Patients assigned to lithium or imipramine continued at the established maintenance level; patients assigned to placebo received placebo capsules identical in appearance to those used for active medication. Patients returned to the hospital every 4 weeks to be rated, obtain medication, and have their serum lithium levels monitored (to maintain levels of .5–1.4 mEq/L). As with the companion study, an affective episode was defined as a manic or depressive attack requiring hospitalization or treatment on an outpatient basis with supplementary medication. Results are summarized in Table 1. Relapses into mania or depression were both three times more common in the placebo group than in the lithium group; however, the difference was significant only for depressive episodes. Furthermore, in both the lithium-treated and the placebo groups, most affective episodes were depressive.

Notably, bipolar patients from the second Prien companion study had a different ratio of manic to depressive episodes (1:2) during the trial period than did bipolar patients from the first study (ratio 2:1). This was true of both the lithium and placebo groups. The investigators (Prien et al 1974) concluded that clinicians should be particularly alert for manic episodes in patients with a recent history of mania and for depressive episodes in patients with a recent history of depression. Moreover, this differential rate of depressive and manic relapses occurred in months 1–4 and 5–24, suggesting that the relapse was not just a continuation of the index episode (Quitkin et al 1986). In addition, the latter analysis addresses the criticisms leveled against the older lithium maintenance designs that abruptly discontinued lithium at the time of randomization and, as a result, increased the risk of relapse into the index episode as a rebound phenomenon.

In addition to the placebo-controlled studies reviewed by Goodwin and Jamison (1990) shown in Table 1, Quitkin et al (1986) discuss two studies that did not include placebo controls but which nevertheless bear upon the issue of index episode and outcome. In a 1981 study by Quitkin et al (1981), patients with either a manic or depressive index episode were randomly assigned to two treatments: lithium ($n = 38$) or lithium plus imipramine ($n = 37$). "Failure" was defined as an episode meeting research diagnostic criteria for major depression, mania, minor depression (4 weeks or more), or hypomania (1 week or more). After a study period of 18–24 months, patients whose index episode was depressed had significantly more depressive relapses (6 of 35 patients) than those whose index episode was manic (1 of 36 patients). These differential outcomes were found regardless of treatment.

Similar results emerged from a subsequent NIMH collaborative study (Prien et al 1984). This involved double-blind, random assignment to three treatments, after stabilization of the acute episode (lithium, $n = 42$; imipramine, $n = 36$; lithium + imipramine, $n = 36$). Failure was defined in three ways: 1) the patient was unable to complete 8 consecutive weeks in the study without recurrence (manic/mixed or depressive); or 2) the patient was able to complete 8 consecutive study weeks but

Table 1. Published, Double-Blind, Placebo-Controlled Trials of Long-Term Treatment in Bipolar Disorder

Investigators (Year)	Design	Index Episode	Trial Period (mo)	Treatment	*n*	No. of Total Failures (%)	No. of Manic Failures (%)	No. of Depressive Failures (%)	Risk of Relapsing into the Presenting Episode After Assignment to PBO (confidence interval)
Baastrup et al (1970)	Discontinuation study of Li responders. "Failure" = hospitalization or use of nonstudy drug	—	5	Li	28	0	0	0	1.6 (.4–6.1)
				PBO	22	12 (55)	7 (32)	5 (23)	
Cundall et al (1972)	Outpatients on Li, half switched to PBO, with crossover after 6 mo. "Failure" = hospitalization or use of nonstudy drug	—	6	Li	12	4 (33)	1 (8)	3 (25)	4.2 (.7–23.9)
				PBO	12	10 (83)	9 (75)	5 (42)	
Stallone et al (1973)	Outpatients in "normal" interval phase (some on Li at entry) randomly assigned to Li or PBO group. "Failure" = episode requiring nonstudy drug	—	28	Li	25	11 (44)	5 (20)	7 (28)	1.4 (.5–3.9)
				PBO	27	25 (93)	15 (55)	13 (48)	
Prien et al[a] (Prien 1973a)	Random assignments to two treatments, after hospitalization for acute mania. Patient considered "relapsed" if he or she had manic or depressive attack requiring hospitalization or supplementary (nonstudy) drugs	Mania	24	Li	101	42 (42)	32 (32)	16 (16)	6.1 (3.4–11.2)
				PBO	104	83 (80)	71 (68)	27 (26)	
Prien et al[a] (1973b, 1974)	Random assignments to three treatments, after hospitalization for acute depression. Main treatment outcome was occurrence of manic or depressive attack requiring hospitalization or outpatient treatment with supplementary drugs.	Depression	24	Li	18	5 (28)	2 (11)	4 (22)	2.6 (.5–12.4)
				IMI	13	10 (77)	7 (54)	4 (31)	
				PBO	13	10 (77)	5 (38)	8 (62)	
Fieve et al (1976)	Prospective design; patients (bipolar I and II) assigned randomly to treatment condition. Number of mood episodes and hospitalizations studied.	Mania	18–40	Bipolar I:					21.3 (2.3–195.8)
				Li	17	15	10 (59)	5 (29)	
				PBO	18	25	17 (94)	8 (44)	
				Bipolar II:					
				Li	7	4 (57)	0	4 (57)	.02 (.001–.4)
				PBO	11	8 (73)	1 (9)	7 (64)	
Dunner et al (1976)	Prospective design, mainly bipolar II patients (consecutively admitted to outpatient clinic) assigned randomly to treatment condition. Relapse defined as requiring supplemental medication	Mania	17 (mean)	Li	16	9	1 (6)	8 (50)	.47 (.1–1.6)
			15 (mean)	PBO	24	16	6 (25)	10 (42)	
Quitkin et al (1978)	Prospective design; bipolar II patients assigned randomly to treatment condition	Mania	10	Li	3	0		0	NA
			5	PBO	3	2 (67)		2 (67)	
Bowden et al (2000)	Prospective design: bipolar I patients assigned randomly to treatment condition	Mania	12	Dvpx	187	45 (24)	33 (18)	12 (6)	1.5 (.7–3.2)
				Li	91	28 (21)	19 (21)	9 (10)	
				PBO	94	36 (38)	21 (22)	15 (16)	
Bowden et al (2003)	Prospective design in bipolar I outpatients with random assignment to Lam, Li, and PBO	Mania	18	Lam	59	28 (47)	20 (34)	8 (14)	1.3 (.8–4.0)
				Li	46	18 (39)	8 (17)	10 (22)	
				PBO	70	49 (70)	28 (40)	21 (30)	
Calabrese et al (2003)	Prospective design in bipolar I outpatients with random assignment to Lam, Li, and PBO	Depression	18	Lam	165	83 (50)	26 (16)	57 (35)	3.4 (2.0–6.3)
				Li	120	56 (47)	10 (8)	46 (38)	
				PBO	119	66 (55)	19 (16)	47 (39)	

PBO, placebo; Li, lithium; —, no index episode studied; IMI, imipramine; Dvpx, divalproex; Lam = lamotrigine; NA = not applicable.
[a]Companion studies.

subsequently had a recurrence; or 3) the patient had no recurrence but terminated for adverse reactions or worsening clinical condition. After a study period of 24 months, the researchers found a higher incidence of manic recurrence in patients whose most recent episode was manic than in those with a depressive index episode. Depressive relapse was more frequent for patients with a depressive index episode; however, the results did not reach statistical significance (Quitkin et al 1986). Treatment outcome was also significantly related to the polarity of the episode that brought the patient into the study.

Finally, Akiskal et al (1985) studied 68 referred juvenile offspring or siblings of adult bipolar patients. Within this cohort, 24 patients presented with a depressive index episode and 11 with a manic or mixed index episode. Recurrent mood episodes were seen in 71% over a 3-year follow-up period. For those whose index episode was depressed, there were 42 subsequent depressive episodes, compared with 30 subsequent manic episodes. For those whose index episode was manic/mixed, there were 18 subsequent depressive episodes and 18 subsequent manic episodes. The higher rate of depressive relapse among those with a depressed index episode is consistent with the other data we have reviewed. However, it is difficult to draw firm conclusions from this study because 1) there was no placebo group; and 2) those with initial depressive index episodes were treated with a tricyclic, whereas those with a manic/mixed index episodes were treated with lithium.

Most prophylaxis studies reviewed by Quitkin et al (1986) did not provide data bearing on the relationship of the index episode to the subsequent episode. Nevertheless, the general findings of Quitkin et al have important implications for drug outcome studies; for example, the investigators observed that a high proportion of manic-prone patients might be included in a lithium prophylactic trial, which was the case in the second Prien companion study (Prien et al 1973a). Such a study might result in an artificially high rate of success with lithium, if lithium were more effective for mania than depression.

Data from at least 15 controlled or partially controlled maintenance studies of carbamazepine in bipolar disorder are available, but the numbers of patients randomly assigned to parallel groups including a placebo arm were small (see Ketter et al 2004 for a summary of this literature). In only one study did the investigators randomly assign 12 patients to carbamazepine and 9 to placebo (Okuma et al 1981). In addition, most of these studies suffer from major methodologic problems, such as the uncontrolled use of adjunctive medications for breakthrough symptoms and the lack of reporting of relapse rates after the index episode by phase of illness. There is one complicated longitudinal study, reported by Denicoff et al (1997), in which 19 recently hypomanic patients with bipolar II disorder and 33 recently manic patients with bipolar I disorder were randomly assigned in a double-blind design for an intended 1 year of treatment with lithium or carbamazepine, with a crossover to the opposite drug in the second year, and then a third year on the combination. The mean number of episodes per year over each of the 3 years by phase of illness was reported (favoring more episodes of hypomania or mania), but the polarity of the first relapse after the index episode was not reported.

Until 2000 (Bowden et al 2000), there had been no placebo-controlled maintenance studies assessing the long-term efficacy of divalproex in bipolar disorder. In one prior open, randomized, controlled trial, valpromide was compared with lithium in the prophylaxis of a mixed cohort of patients, including unipolar (n = 29) and bipolar disorder (n = 121) patients (Lambert and Venaud 1992). This study reported the number of manic and depressive episodes in the year before randomization (manic: lithium = 104, valpromide = 180; depressive: lithium = 178, valpromide = 131) and during the year of random assignment (manic: lithium = 15, valpromide = 14; depressive: lithium = 28, valpromide = 25). The number of mood episodes was .51 per subjects randomized to valpromide and .61 for those assigned to lithium. For both drugs, the efficacy was slightly higher in preventing mania than depression. The design of this study and the other open, long-term studies of various preparations of valproate do not permit a meaningful analysis of the polarity of the index episode as a predictor of the polarity of relapse.

Naturalistic Studies Since 1990

Only a handful of maintenance studies of bipolar outcome for which the relationship of index episode to recurrence or relapse might be determined have appeared since 1986. These studies vary considerably in methodology, ranging from naturalistic studies of relapse rates in recently manic patients to prospective, placebo-controlled studies of recently depressed bipolar patients.

Strober et al (1990) carried out an 18-month, naturalistic prospective study of relapse after discontinuation of lithium maintenance in 37 adolescents with bipolar I disorder manic type. The subjects' illness had been stabilized with lithium carbonate during inpatient hospitalization. Thirteen patients discontinued lithium shortly after discharge. Not surprisingly, the relapse rate of bipolar illness in these 13 patients was nearly three times higher than in those who continued lithium prophylaxis. The investigators did not provide follow-up data on the polarity of relapses among the noncompleters. Among the completers (n = 24), 14 relapses occurred over the 18-month study period. Fifty percent of relapses were manic (n = 7); 29% were depressive (n = 4); and 21% were mixed (n = 3). Hence, although no single type of relapse occurred in the majority of cases, the most common relapse subtype was manic, consistent with predictions based on the index episode.

Turvey et al (1999) examined polarity sequence across multiple episodes among mainly bipolar I patients followed prospectively in a naturalistic study for up to 15 years as part of the NIMH Collaborative Study of depression. Episodes were categorized according to the number of phases (mono-, bi-, or polyphasic) and the polarity of the initial phase (manic or depressive). A monophasic episode was exclusively manic, hypomanic, or depressive, with no switching between poles or mixed symptoms. Biphasic episodes consisted of one manic or hypomanic phase and one major depressive phase, not necessarily in that order. A polyphasic episode had at least two switches in polarity. Turvey et al (1999) found that affective polarity at onset for the first episode was associated with polarity at onset for the remaining three episodes. Specifically, patients whose first prospectively observed episode began with a manic phase had approximately a 75% chance of having a similar episode at recurrence. Conversely, a depressive onset increased the likelihood (55%–60%) of having episodes starting with a depressive phase in subsequent episodes. The agreement in polarity at the beginning of an episode did not diminish over subsequent recurrences. The investigators concluded that in bipolar I patients, affective polarity at episode onset was associated with the initial polarity in subsequent episodes. Furthermore, the index episode polarity tended to predict duration of subsequent episodes—perhaps because a higher proportion of episodes

beginning with depression were polyphasic, whereas episodes beginning with mania were more likely biphasic. Thus, the investigators opined that the association between the depressive-manic-well interval polarity sequence and higher morbidity might result from the tendency of depressive episodes to yield cycling episodes of long duration. In effect, episodes beginning with depression might be more likely to presage "switching" over the course of the four prospectively observed episodes, compared with episodes beginning with mania. Such mood instability could be linked with greater psychiatric morbidity and dysfunction. In addition to its naturalistic design, another limitation of the Turvey et al study was the recruitment of patients at varying times during the course of their illness, possibly conflating subjects with differing polarity predominance (Turvey et al 1999).

Recently, Altshuler et al (2003) carried out a naturalistic, nonrandomized, follow-up study (the Stanley Bipolar Treatment Network) of 84 bipolar patients (mainly types I and II) who had achieved remission from a depressive episode with the addition of an antidepressant to an ongoing mood stabilizer regimen. Subjects were followed prospectively for 1 year. The risk of depressive relapse among 43 subjects who stopped antidepressant treatment within 6 months after remission was compared with the risk among 41 subjects who continued antidepressants beyond 6 months. The investigators found that 1 year after having experienced a good response to antidepressant therapy, 70% of patients who discontinued antidepressant therapy had a depressive relapse, compared with 36% of patients who continued taking antidepressants. Overall, there were fewer manic relapses than depressive relapses (15 patients [18%] experiencing mania, 36 patients [43%] experiencing depression), suggesting that at 1 year after successful treatment of a depressive index episode, the risk of relapse into depression is higher than the risk of relapse into mania. To explore the effects of other factors on the likelihood of relapse, the investigators pooled the continuers and discontinuers and performed an overall comparison of those who had relapsed with those who had not. The variables assessed included the number and type of mood stabilizers, the type of bipolar diagnosis, the number and polarity of previous mood episodes, age at onset, family history, and duration of illness. None of these variables was significantly associated with greater risk for depressive relapse. Notably, there were no rapid cyclers in the cohort of patients responding to treatment with antidepressants (personal communication with the authors, 2003). It is also difficult to generalize from this study, because the treatment groups were initially selected on the basis of a good response to antidepressant augmentation; in other words, patients who had dysphoric or hypomanic reactions were systematically excluded from the study.

Information about depressive symptoms during the index episode might provide another perspective on subsequent mood episodes. Zarate et al (2001) compared two groups of patients with an index episode of mania: 1) 28 patients with a first episode of mania who cycled into a major depressive episode without recovery from their index episode; and 2) 148 patients with first-episode mania who did not cycle into depression. Approximately 16% (28 patients) of the entire cohort ($N = 176$) cycled into major depression. This group was more likely to have higher depressive scores at admission and tended to have the mixed subtype of BPD. Specifically, a higher Hamilton Depression Scale total score at admission was associated with a greater risk of cycling into depression. In one sense, this is consistent with the "depression breeds depression" hypothesis; in other words, even when the index episode is not depressive in nature, the dimension of depression might still predict depressive outcome. However, the Zarate et al (2001) study is not directly comparable to those in which patients had recovered from their index episode.

In the McLean-Harvard First-Episode Mania study (Tohen et al 2003), the investigators evaluated recovery, first recurrence, and new illness onset after first hospitalization for mania. Bipolar disorder I patients ($N = 166$) were followed for 2–4 years after their first hospitalization for a manic or mixed episode to assess timing and predictors of outcomes. Three were measured: syndromal (DSM-IV criteria for disorder no longer met), symptomatic (Young Mania Rating Scale score ≤ 5 and Hamilton Depression Rating Scale score ≤ 8), and functional (regaining of premorbid occupational and residential status). Rates of remission (syndromal recovery sustained ≥ 8 weeks), switching (onset of new dissimilar illness before recovery), relapse (new episode of mania within 8 weeks of syndromal recovery), and recurrence (new episode after remission) were also assessed. By 2 years, 98% of subjects achieved syndromal recovery, and 72% achieved symptomatic recovery, but only 43% achieved functional recovery. Within 2 years of syndromal recovery, 40% experienced a new episode of mania (20%) or depression (20%), and 19% switched phases without recovery. Predictors of mania recurrence were initial mood-congruent psychosis, lower premorbid occupational status, and initial manic presentation. Predictors of depression onset were higher occupational status, initial mixed presentation, and any comorbidity. The investigators concluded that risks of new manic and depressive episodes were similar but were predicted by contrasting factors. The results of this study suggest that the hypothesis under consideration might not apply to first episodes of mania under standard treatment conditions.

Finally, there is compelling evidence that comorbidity in bipolar I disorder is associated with a high number of mixed features, depressive episodes, and suicide attempts, thus strongly influencing course and outcome (Vieta et al 2001). The extent to which comorbidity impacts on the ability of the index episode to predict the polarity of relapse during treatment is unclear, however, because most double-blind, placebo-controlled, long-term studies in bipolar disorder have excluded patients with Axis I comorbidity, especially substance use disorders.

Randomized, Placebo-Controlled Studies Since 1986

There have been only three published randomized, placebo-controlled, double-blind, parallel-group, long-term studies of bipolar I outcome (Bowden et al 2000, 2003; Calabrese et al 2003) since Quitkin et al's 1986 review (Quitkin et al 1986). Bowden et al (2000) carried out a 52-week, randomized, placebo-controlled, double-blind, parallel-group trial comparing divalproex with placebo and lithium in the maintenance treatment of bipolar I disorder with index manic episode. The primary outcome measure was time to recurrence of any mood episode. For randomized patients ($N = 372$), premature termination due to any mood episode was predominantly for manic relapse in all treatment groups. Specifically, in the divalproex group ($n = 187$), 33 patients (18%) terminated prematurely owing to a manic episode, compared with 12 (6%) for depression. In the lithium group ($n = 91$), the corresponding values were 19 manic (21%) versus 9 depressed (10%); and in the placebo group ($n = 94$), 21 (22%) manic versus 15 (16%) depressed. This study tends to confirm the hypothesis that index episode predicts subsequent episode polarity, at least when premature termination is used as the episode criterion.

A separate analysis of the Bowden et al (2000) data by Gyulai et al (2003) examined depressive relapse risk. The study used an outcome measure called "breakthrough depression," which was defined by either 1) the need for an "add-on" antidepressant; or 2) discontinuation from the study because of depression. (Note that this construct is not identical to a DSM-IV episode of major depression.) The Gyulai et al (2003) study found that 28% of placebo-treated patients (26 of 94) had breakthrough depression; in other words, they met one or both of the aforementioned criteria. This rate was lower than in previous double-blind, placebo-controlled studies of lithium (approximately 44%–50%), perhaps owing to the relatively slow tapering off of lithium (over 2 weeks) in the Gyulai study. Notably, depressive relapse for the intent-to-treat sample as a whole was predicted by a higher lifetime number of both manic and depressive episodes. The investigators observed that theirs was the first study to suggest that the lifetime number of manic episodes is associated with continuing depressive morbidity in BPD. These data suggest that although depression does breed depression, other factors might also worsen depressive morbidity.

Since 1990, there have been only two published, randomized, placebo-controlled companion studies of putative mood stabilizers, with respect to bipolar outcome. Bowden et al (2003) carried out a placebo-controlled, 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. After an 8–16-week open-label phase, patients were randomized to lamotrigine, lithium, or placebo under double-blind conditions, for up to 18 months. In the event of a mood episode, antidepressants, antipsychotics, benzodiazepines, anticonvulsants, and mood stabilizers or electroconvulsive therapy (ECT) were administered as treatment intervention (the primary study end point). Among patients experiencing mood episodes that required intervention during the double-blind phase, elevated mood episodes were more frequent than depressive episodes for the lamotrigine and placebo groups. Of the 49 interventions in the placebo group, 28 (57%) were for mood elevation (mania, hypomania, or mixed), compared with 21 (43%) for depression. In contrast, depressive episodes outnumbered elevated episodes in the lithium group. The investigators commented that the proportion of manic relapses in all groups might have been influenced by the limitation of the study to patients who had experienced recent manic or hypomanic episodes.

Indeed, in light of the hypothesis that "mania begets mania, depression begets depression," Calabrese et al (2003) undertook a similarly designed study, which enrolled bipolar patients with a recent episode of depression. This was a placebo-controlled, 18-month trial of lamotrigine and lithium maintenance in recently depressed bipolar I patients. During an 8–16-week open-label phase, lamotrigine (titrated to 200 mg/day) was added to current therapy for currently or recently depressed bipolar I outpatients (n = 966), and concomitant drugs were gradually withdrawn. Patients stabilized on open-label treatment (n = 463) were randomized to lamotrigine (50, 200, or 400 mg/day), lithium (.8–1.1 mEq/L), or placebo monotherapy. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed). Clinic visits were scheduled weekly during the first 4 weeks of the double-blind phase, biweekly through week 8, and every 4 weeks thereafter through week 76. At each clinic visit, psychiatric evaluations from the screening visit were repeated and adverse events assessed. Patients could be treated with added antidepressants, antipsychotics, anticonvulsants/mood stabilizers, or ECT if the treating psychiatrist determined clinically that developing illness symptomatology required such additional intervention. The time to this treatment intervention was the primary outcome measure; however, short-term, intermittent use of rescue medications was permitted, including the use of chloral hydrate (up to 2 g/day), lorazepam (up to 1 mg/day), temazepam (up to 10 mg/day), oxazepam (up to 30 mg/day), or midazolam (up to 15 mg/day) for control of agitation, irritability, restlessness, insomnia, or hostile behavior without triggering the primary study end point. After reaching the primary study end point, patients were permitted to continue double-blinded study medications and to be augmented with open-label psychotropic medications other than lithium or lamotrigine up to week 52 and were then discontinued from the study. Those patients who had not yet reached primary study end point were continued in the study through week 76.

Consistent with the index episode hypothesis, interventions for emerging symptoms of depression outnumbered interventions for manic symptoms by nearly 3 to 1. The total number of interventions for depression (all treatment groups) was 170, versus 67 for mania. In the placebo group, the interventions were 47 for depression, versus 19 for mania. The overall ratio of depressive to manic interventions was about 2.5, consistent with Veterans Administration–NIMH collaborative studies.

The Bowden et al (2003) and Calabrese et al (2003) studies stand in contrast to most of the early maintenance studies conducted in the 1970s, which evaluated the proportion of patients exhibiting a full relapse, usually severe enough to require hospitalization. In these older studies, earlier intervention was not permitted. The Bowden et al (2003) and Calabrese et al (2003) studies did not require hospitalization for a subject to reach study endpoint. The primary end point—treatment intervention—was selected to improve the sensitivity of the primary outcome measure by lowering the threshold for a treatment "failure." This end point minimized patient exposure to placebo and spared patients the risks associated with full affective relapse. It is possible, of course, that a higher threshold might have reduced the ratio of depressive to manic interventions.

Conclusion

Given the small sample sizes of individual studies and the limited number of placebo-controlled maintenances involving depressive index episodes, conclusions regarding the impact of the index episode on the polarity of relapse should be considered provisional. Nevertheless, most of the evidence from both the pre-lithium and modern eras suggests that the index episode tends to predict the polarity of the subsequent major mood episode. In general, "like breeds like"; that is, a manic index episode tends to predict a manic relapse, whereas a depressive index episode predicts a depressive relapse. As Quitkin et al (1986) pointed out nearly 2 decades ago, this interaction between type of index episode and treatment outcome requires that trials of maintenance therapy stratify patients according to manic or depressive index episode. The only medications that have been evaluated in similarly designed placebo-controlled maintenance studies involving both recently manic and recently depressed patients have been lithium and lamotrigine (Prien et al 1973a, 1973b; Bowden et al 2003; Calabrese et al 2003). The paucity of such studies is in contrast to the emerging consensus regarding the magnitude of the unmet need in bipolar depression.

With respect to the controversy surrounding use of antide-

pressants in bipolar depression (Altshuler et al 2003; Ghaemi et al 2000), our findings do not provide direct evidence for, or against, this practice; however, our findings could suggest that prevention of depressive bouts, or vigorous treatment of the index depressive episode, might reduce the likelihood of another depressive episode on the next admission. The hypothesis under consideration is "drug-neutral."

We conclude that the predictive value of the polarity of the index episode has important implications for the development of mood stabilizers and believe that before an agent's spectrum of mood-stabilizing properties can be fully understood or generalized, studies involving both manic and depressive index episodes must be conducted, either through separate studies or a properly powered study that stratifies for the index episode.

This research is supported by National Institute of Mental Health Grant P20 66054 and an unrestricted grant from GlaxoSmithKline, Inc.

Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB (1985): Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. *Arch Gen Psychiatry* 42:996–1003.

Altshuler L, Suppes T, Black D, Nolen WA, Keck PE Jr, Frye MA, et al (2003): Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry* 160:1252–1262.

Altshuler LL, Frye MA, Gitlin MJ (2003): Acceleration and augmentation strategies for treating bipolar depression. *Biol Psychiatry* 53:691–700.

Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A (1970): Prophylactic lithium: Double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet* 2:326–330.

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al (2000): A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 57:481–489.

Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, et al (2003): A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 60:392–400.

Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, et al (2003): A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 64:1013–1024.

Cundall RL, Brooks PW, Murray LG (1972): A controlled evaluation of lithium prophylaxis in affective disorders. *Psychol Med* 2:308–311.

Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM (1997): Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 58:470–478.

Dunner DL, Stallone F, Fieve RR (1976): Lithium carbonate and affective disorders. V: A double-blind study of prophylaxis of depression in bipolar illness. *Arch Gen Psychiatry* 33:117–120.

Fieve RR, Kumbaraci T, Dunner DL (1976): Lithium prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. *Am J Psychiatry* 133:925–929.

Ghaemi SN, Boiman EE, Goodwin FK (2000): Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *J Clin Psychiatry* 61: 804–808.

Goodwin FK, Jamison KR (1990): Suicide. *Manic-Depressive Illness*. New York: Oxford University Press, 227–246.

Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, et al (2003): Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* 28:1374–1382.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al (2003): A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 60:261–269.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al (2002): The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59:530–537.

Ketter TA, Wang PW, Post RM (2004): Carbamazepine and oxcarbamazepine. In: Schatzberg AF, Nemeroff CB, editors. *Textbook of Psychopharmacology,* 3rd ed. Arlington, Virginia: American Psychiatric Publishing, 581–606.

Lambert PA, Venaud G (1992): Comparative study of valpromide versus lithium in the treatment of bipolar disorder. *Nervure* 5:57–65.

Lundquist G (1945): Prognosis and course of manic-depressive psychoses: A follow-up study of 319 first admissions. *Acta Psychiatr Neurol Suppl* 35:1–96.

Morgan HG (1972): The incidence of depressive symptoms during recovery from hypomania. *Br J Psychiatry* 120:537–539.

Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, et al (1981): A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. *Psychopharmacology (Berl)* 73: 95–96.

Perris C (1968): The course of depressive psychoses. *Acta Psychiatr Scand* 44:238–248.

Prien RF, Caffey EM Jr, Klett CJ (1973a): Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Report of the Veterans Administration and National Institute of Mental Health collaborative study group.* Arch Gen Psychiatry 28:337–341.

Prien RF, Klett CJ, Caffey EM Jr (1973b): Lithium carbonate and imipramine in prevention of affective episodes. *A comparison in recurrent affective illness.* Arch Gen Psychiatry 29:420–425.

Prien RF, Klett CJ, Caffey EM Jr (1974): Lithium prophylaxis in recurrent affective illness. *Am J Psychiatry* 131:198–203.

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, et al (1984): Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Arch Gen Psychiatry* 41:1096–1104.

Quitkin F, Rifkin A, Kane J, Ramos-Lorenzi JR, Klein DF (1978): Prophylactic effect of lithium and imipramine in unipolar and bipolar II patients: A preliminary report. *Am J Psychiatry* 135:570–572.

Quitkin FM, Kane J, Rifkin A, Ramos-Lorenzi JR, Nayak DV (1981): Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. A double-blind study. *Arch Gen Psychiatry* 38:902–907.

Quitkin FM, Rabkin JG, Prien RF (1986): Bipolar disorder: Are there manic-prone and depressive-prone forms? *J Clin Psychopharmacol* 6:167–172.

Shapiro DR, Quitkin FM, Fleiss JL (1989): Response to maintenance therapy in bipolar illness. Effect of index episode. *Arch Gen Psychiatry* 46:401–405.

Stallone F, Shelley E, Mendlewicz J, Fieve RR (1973): The use of lithium in affective disorders. 3. A double-blind study of prophylaxis in bipolar illness. *Am J Psychiatry* 130:1006–1010.

Strober M, Morrell W, Lampert C, Burroughs J (1990): Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: A naturalistic study. *Am J Psychiatry* 147:457–461.

Tohen M, Zarate CA Jr, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, et al (2003): The McLean-Harvard First-Episode Mania Study: Prediction of recovery and first recurrence. *Am J Psychiatry* 160:2099–2107.

Turvey CL, Coryell WH, Arndt S, Solomon DA, Leon AC, Endicott J, et al (1999): Polarity sequence, depression, and chronicity in bipolar I disorder. *J Nerv Ment Dis* 187:181–187.

Vieta E, Colom F, Corbella B, Martinez-Aran A, Reinares M, Benabarre A, et al (2001): Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord* 3:253–258.

Zarate CA Jr, Tohen M, Fletcher K (2001): Cycling into depression from a first episode of mania: A case-comparison study. *Am J Psychiatry* 158:1524–1526.