Strategies for Preventing the Recurrence of Bipolar Disorder

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In interpreting the maintenance literature for bipolar disorder, attention needs to be paid to important methodological issues. In this article, we initially examine the methodological topics that need to be considered, and we then examine the content of the evidence regarding maintenance treatments. Agents used in the long-term treatment of bipolar disorder possess varying degrees of supportive evidence. By consensus, the number of randomized studies and years of clinical experience with lithium mark it as the evidentially strongest long-term agent for bipolar disorder. Recent studies also demonstrate likely long-term benefit with lamotrigine, and possibly olanzapine. Although we possess fewer randomized data, some such evidence exists and, along with clinical experience, supports the likely long-term utility of valproate in the treatment of bipolar disorder as well. Some psychotherapies also may possess adjunctive maintenance efficacy. *(J Clin Psychiatry 2004;65[suppl 10]:16–23)*

METHODOLOGICAL INTRODUCTION

Several methodological guidelines (Table 1)[1] are important to highlight before examining the literature on bipolar maintenance. First, prevention trials for bipolar disorder can be divided into 2 distinct groups: prophylaxis and relapse prevention studies. Prophylaxis trials involve the treatment of patients who are generally considered to be euthymic. Thus, these patients may have been stable for years or recently recovered from an acute depressive or manic episode. In other words, in prophylaxis studies the patients are selected regardless of their last acute mood state, and the study drug is added to assess efficacy in preventing new mood episodes. In contrast, relapse prevention involves patients in an acute episode who are treated openly with the study drug to short-term recovery and who are then randomly assigned to continue active treatment or switch to placebo. This "enriched" study design, commonly used in randomized controlled trials (RCTs) today, is not as generalizable as the classic prophylaxis RCT design, as it is only applicable in the greater population to those patients that begin the drug during an acute episode and then continue treatment after recovery.

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Another methodological issue to highlight is the difference between continuation and maintenance treatments. The acute phase of recovery is commonly defined as the 2 months following recovery from an acute episode. Following this period is the continuation phase, which is defined as months 2 through 6. During the continuation period, the natural course of the episode is still active and discontinuing treatment results in relapse into the existing acute episode. After 6 months of recovery, the maintenance phase begins and can be conceptualized as the time in which the previous acute episode has resolved. During the maintenance phase, the appearance of a mood episode indicates a recurrence of symptoms, i.e., a new acute episode different from the previous. To properly interpret the results of a study, we must distinguish between the continuation and maintenance phase results. For example, in an enriched-design study, positive results within the first 6 months very likely indicate effectiveness in relapse prevention as opposed to true prophylactic efficacy.

The rationale for randomized studies is to remove the effects of confounding factors, i.e., the impact of factors other than the experimental intervention that might lead to the result.[2] Randomization ensures that, except for the experimental factor of interest, all known and unknown factors are equally distributed in the groups studied. One can only compare different results in the same sample if one wants to maintain the benefits of randomization, such as the removal of confounding bias. To directly compare results from different studies would be to commit the "apples and oranges" error, as the results from different studies are not directly comparable due to the variability of potential confounding factors (e.g., age, gender distribution, severity of illness). While it is logical that if drug A is shown in one study to have response rates equivalent to drug B, and drug B is shown to have better efficacy than drug C in

Table 1. Methodological Guidelines for Maintenance Studies of Bipolar Disorder[a]

1. Continuation phase efficacy is not necessarily the same as maintenance efficacy.
2. "Enriched" samples may reflect relapse prevention better than true prophylaxis.
3. Avoid the "apples and oranges" error: do not directly compare frequencies across different studies.
4. It is best to compare experimental drug with active control and placebo in the same sample.
5. The risk of positive findings increases with the number of secondary analyses performed.

[a]Based on Ghaemi and Hsu.[1]

another study, then drug A is equivalent to drug B and better than drug C. This logic, however, is not empirically valid in RCTs. To draw these conclusions, these comparisons would have to be observed in the same study. Thus, the ideal study design for maintenance treatment is composed of 3 arms: the experimental drug, an active control, and placebo.

In interpreting RCTs, it is also important to distinguish primary from secondary outcomes. Primary outcomes are included in the main analysis and should receive the most weight. Secondary outcomes are more liable to be positive by chance, and thus are best seen as exploratory rather than definitive. Often, studies are described according to the positive findings regardless of whether the finding is a primary or a secondary analysis. The p value of .05, otherwise interpreted as a 5% likelihood that this result occurred by chance, applies only to the primary outcome hypothesis. If more than the primary hypothesis is tested, the p value must be adjusted for multiple comparisons, such as with the Bonferroni correction. For example, suppose that in a maintenance study, the primary analysis was negative and the secondary analysis found a positive result with a p value of .025. The Bonferroni correction for multiple comparisons divides the p value by the number of comparisons made to adjust for any false-positive findings. The more comparisons that are made, the smaller the p value needs to be to account for any false-positive findings. If 5 comparisons were made, .05 divided by 5 gives a p value of .01, thus rendering the p value of .025 not significant when taking into account the small number of multiple comparisons.

Below, we review the literature on maintenance treatment of bipolar disorder through an evidence-based and methodologically oriented perspective.

SPECIFIC AGENTS

Historically, lithium has been the medication of choice when treating acute bipolar episodes and, more importantly, in maintenance therapy. Other agents, such as valproate, olanzapine, lamotrigine, and antidepressants, have also been studied recently as primary or adjunctive treatments for the management of bipolar disorder.

Lithium

In a recent review of the literature on lithium,[3] 14 double-blind, randomized studies of lithium in 541 patients were identified in which lithium was found to be efficacious in long-term maintenance treatment of bipolar disorder. Although most of the studies were limited by a high dropout rate, lithium was found to be effective in reducing mania and affective morbidity associated with bipolar disorder. Recent studies using a gradual discontinuation design also suggest similar efficacy. Three studies[3] using a gradual discontinuation design among 1010 patients have suggested efficacy with lithium.

Rapid cycling occurs in 10% to 20% of patients diagnosed with bipolar disorder.[4] These patients may be inherently treatment refractory and less responsive to prescribed treatment when compared with patients who do not suffer from rapid cycling.[5] Between 72% and 82% of patients who suffer from rapid cycling have shown poor response to lithium treatment,[6] and it has been hypothesized that patients with rapid cycling may respond better to anticonvulsant than lithium treatment. A recent meta-analysis,[5] however, of 16 studies compared the efficacy of various mood stabilizers in 1856 bipolar patients with and without rapid cycling. All of the studies included patients who had been treated for at least 4 months and had suffered from at least 4 recurrences of mania or depression within the previous year. The mean length of treatment time was 47.5 months, and prevalence of rapid cycling was estimated at 15.4%. The rates of recurrence and clinical nonimprovement were more than twice as high on average in rapid cycling patients than patients without rapid cycling, with anticonvulsants and lithium having similar efficacy. The pooled recurrence rates per month were in fact lower with lithium (2.09%) than with valproate (3.63%) or lamotrigine (8.5%), although there was great variability in the data.

Divalproex

Two studies[7,8] have focused on long-term trials of divalproex. Bowden and colleagues[7] conducted a double-blind, parallel-group, multicenter RCT comparing the efficacy of divalproex, lithium, and placebo as prophylactic treatment over 52 weeks. Patients meeting DSM-III-R criteria for bipolar depression were randomly assigned to maintenance treatment with divalproex (N = 187), lithium (N = 91), or placebo (N = 94). All participants were between 18 and 75 years of age, with an index manic episode as diagnosed by the DSM-III-R, and had suffered from at least 1 other manic episode in the past 3 years. Manic episodes were defined either as a Mania Rating Scale score of ≥ 16 or as an episode requiring hospitalization. Depressive episodes were defined as requiring antidepressant treatment or premature discontinuation from the study because of depressive symptoms. The primary outcome measure was time to any mood episode. Doses, which were gradually increased on the basis of body weight and serum trough concentra-

tions, were maintained at 71 to 125 μg/mL for divalproex and 0.8 to 1.2 mmol/L for lithium. The primary outcome was negative: both divalproex and lithium were similar to placebo in the time to onset of another full mood episode, while secondary analyses suggested a potential benefit with divalproex in prevention of depressive episodes.

In another recent double-blind, randomized, maintenance study[8] of rapid cycling in bipolar disorder, divalproex or lithium was administered to 61 patients over 20 months. Divalproex delayed relapse somewhat compared with lithium, but the difference was not statistically significant. Due to the small sample size and increasing patient dropouts over time, there was a large risk of a type II, false negative error in this study.

Olanzapine

Olanzapine has been shown to be effective in treating acute mania, and researchers have sought to examine the long-term benefits of olanzapine treatment. Recent maintenance studies have compared olanzapine directly to valproate and lithium,[9] added to valproate or lithium,[10] and as monotherapy compared with placebo.[11] It is important to note that the olanzapine studies did not use the ideal 3-arm treatment design (olanzapine vs. active control vs. placebo), and thus the results are not conclusive.

Tohen and colleagues[12] studied the efficacy of olanzapine and divalproex in 251 patients. Participants in this double-blind study were between the ages of 18 and 75 years and had a DSM-IV diagnosis of manic or mixed episode bipolar disorder and a baseline score of at least 20 on the Young Mania Rating Scale (YMRS). Patients were randomly assigned to olanzapine (N = 125) or divalproex (N = 126) for a period of 47 weeks. The initial doses were 15 mg/day of olanzapine (mean modal dose = 16.2 mg/day) and 750 mg/day of divalproex (mean modal dose = 1584.7 mg/day). Dose adjustments were based on clinical response, serum concentrations, and adverse events. Symptomatic remission of mania and depression was defined as an endpoint total YMRS score of 12 and a Hamilton Rating Scale for Depression (HAM-D) score ≤ 8. Severity of symptoms was assessed using the 11-item YMRS and the 21-item HAM-D, and severity of illness was rated on the Clinical Global Impressions scale (CGI) for Bipolar Illness and the Positive and Negative Syndrome Scale. In the primary outcome, time to symptomatic remission for manic and depressive symptoms between the 2 groups was similar, and the rates of remission were greater in both groups at endpoint than at 3 weeks. Among secondary outcomes, symptomatic and syndromal remission of mania was reduced significantly sooner with olanzapine than with divalproex. However, 84% of the sample discontinued treatment, which suggests both treatments might have been equally ineffective. Further, due to the absence of a placebo group, one cannot assess whether either agent was effective.

In an olanzapine versus lithium maintenance study,[13] 431 patients meeting the symptomatic remission criteria after a 6- to 12-week, open-label, combination treatment with both agents were then randomly assigned to one treatment. The double-blind trial lasted 52 weeks, with relapse defined as a YMRS total score ≥ 15 and/or a 21-item HAM-D total score ≥ 15. Patients were treated with 5 to 20 mg/day of olanzapine (N = 217) or 300 to 1800 mg/day of lithium (N = 214). In the primary outcome, the relapse rate was slightly lower in the olanzapine-treated group (30%) than the lithium-treated group (38.8%). Among secondary outcomes, olanzapine-treated patients had a lower incidence of relapse into manic episodes than lithium-treated patients (14.3% vs. 28.0%). However, both groups had similar incidences of depression relapse. The overall dropout rate was 60.3% in 1 year, but more olanzapine-treated patients (46.5%) than lithium-treated patients (32.7%) completed the study. High dropout rates make the statistical comparisons difficult to interpret, but in this study[13] the dropout rates were somewhat lower than in the divalproex-olanzapine study.[12] Again, the absence of a placebo group precludes definitive interpretation of efficacy, although this study[13] is suggestive of similar results in this relapse-prevention design for acutely manic patients who were initially responsive to olanzapine. These data cannot be generalized to the entire population of patients with bipolar disorder.

One maintenance adjunctive treatment trial[10] has been conducted with olanzapine. Olanzapine (N = 30) or placebo (N = 38) was combined with either valproate or lithium for 18 months to determine whether olanzapine augmentation would reduce symptomatic relapse among bipolar patients. In the primary analysis, there was no benefit in the olanzapine group compared with the placebo group in time to a mood episode among syndromal responders. In one of the secondary analyses, those who achieved complete remission for the treatment of acute manic episodes appeared to show an increase in survival time until symptomatic recurrence was seen. Thus, in terms of syndromal recurrence, there was no difference in the total samples. In terms of symptomatic recurrence, however, there may have been benefit in the combination of olanzapine with valproate or lithium among patients who had complete remission of the acute mania phase. One might then conclude that if a patient responds completely to olanzapine plus a mood stabilizer for acute mania and has very few manic symptoms after a month or two of treatment, then there might be a long-term benefit in continuation of the agent. However, the side effect disadvantage with olanzapine treatment was weight gain, with a 20% incidence of weight gain seen in the olanzapine combination group versus a 2% incidence of weight gain in the placebo combination group.

In the last maintenance RCT with olanzapine,[11] patients were openly treated for acute mania with olanzapine and

then randomly assigned to long-term, double-blind, treatment with olanzapine (N = 225) or placebo (N = 136). Relapse was defined as a YMRS total score ≥ 15, and/or a 21-item HAM-D total score ≥ 15, and/or psychiatric hospitalization. In the primary outcome, the majority of placebo-treated patients appeared to rapidly relapse within 1 or 2 months after randomization, while time to relapse was significantly longer in the olanzapine-treated patients ($p < .001$). After 1 year of follow-up, relapse to an affective episode occurred in 46.7% of olanzapine-treated patients compared with 80.1% of placebo-treated patients. Among secondary outcomes, olanzapine-treated patients had a lower rate of relapse into manic episodes (16.4%) when compared with placebo-treated patients (41.2%). The main benefit with olanzapine appeared to occur in the continuation phase (within 2 months after resolution of acute mania). In other words, there was rapid relapse after discontinuation of olanzapine within 2 months of recovery from acute mania. Whether this continuation-phase benefit translates into long-term prophylactic benefit is unclear.

Lamotrigine

Lamotrigine has been studied as a maintenance treatment for bipolar I disorder, especially in patients with recurring depressive episodes.[14]

One randomized, double-blind, parallel-group study[14] observed the efficacy of lithium versus lamotrigine versus placebo as maintenance treatment for bipolar patients with recent depression. Participants had to be at least 18 years of age and have a DSM-IV diagnosis of bipolar I disorder with a clinical interview or most recent mood episode occurring within 60 days of the screening visit. Participants also had to have a history of at least 1 manic or hypomanic episode within 3 years before study enrollment and at least 1 additional depressive episode, including mixed episode, within 3 years of enrollment. After an open-label phase of 8 to 16 weeks, all participants who had reached a stable dose of lamotrigine and had maintained a CGI-Severity (CGI-S) score ≤ 3 for 4 weeks (N = 463) were eligible for the double-blind, randomization phase of this trial.

Patients were randomly assigned to 1 of 5 treatment groups—lamotrigine, 50, 200, or 400 mg/day; lithium, titrated to serum levels of 0.8 to 1.1 mEq/L; or placebo—for a period of 18 months, with 221 patients in the lamotrigine group, 121 in the lithium group, and 121 in the placebo group.[14] The primary efficacy endpoint measure was time to intervention with any other type of treatment, and the secondary efficacy endpoint measure was time to intervention for any manic, hypomanic, or depressive episode or a mean change from baseline according to the HAM-D, Mania Rating Scale (MRS), CGI-S, or Global Assessment Scale (GAS) scores. The rates of discontinuation classified by reason were similar across treatment groups, although lithium tended to have a higher rate of discontinuation due to adverse effects than the other 2 treatment groups. In the primary analysis, both lithium and lamotrigine were significantly superior to placebo in delaying time to intervention for any mood episode. Median survival times were 200 days for lamotrigine, 170 days for lithium, and 93 days for placebo. In secondary analyses, lithium was found to be statistically superior to placebo in prolonging time to intervention in manic or hypomanic episodes, while lamotrigine was found to be superior to placebo in prolonging the time to intervention for depressive episodes. After adjusting for the number of analyses performed with the Bonferroni correction, these results would not be statistically significant.

A similar randomized, double-blind, parallel-group study[15] assessed the efficacy of lamotrigine versus lithium versus placebo as maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Patients had to be at least 18 years of age and have a DSM-IV diagnosis of bipolar I disorder. The most recent clinical interview and/or mood episode must have been within the past 60 days of enrollment, and participants must have had a history of at least 1 manic or hypomanic episode, and 1 additional depressive episode, including mixed episode, within 3 years before study enrollment. After an open-label phase of 8 to 16 weeks, all participants who had reached a stable dose of lamotrigine while maintaining a CGI-S score ≤ 3 for 4 weeks (N = 175) were then eligible for the double-blind randomization phase of this trial (lamotrigine, 59 patients; lithium, 46 patients; placebo, 70 patients). Similar to the Calabrese et al. study,[14] eligible patients were randomly assigned to 1 of 5 treatment groups: lamotrigine, 100, 200, or 400 mg/day; lithium, titrated to serum levels of 0.8 to 1.1 mEq/L; or placebo for a period of up to 19 months. Again, the primary efficacy endpoint measure was time to intervention with any other type of treatment, and the secondary efficacy endpoint measures were time to early discontinuation; time to intervention for any manic, hypomanic, mixed episode, or depressive episode; or a mean change from baseline on the MRS, HAM-D, CGI, or GAS scales during the double-blind phase of the study.

Of the 175 randomized patients, 35 patients discontinued due to adverse events. For these patients, the mean duration of time spent in the study was 300 days (SD = 115; range, 136–582 days). Among the rest of the randomized group, excluding natural endpoints, discontinuation rates were higher in the lithium group (24%) due to adverse events as compared with the other 2 groups (lamotrigine or placebo) and in the lamotrigine group (7%) for withdrawal of consent. Both lithium and lamotrigine were superior to placebo in delaying time to intervention for any mood episode ($p = .003$ and $p = .02$, respectively) and did not differ from each other for this variable. Median survival times were 85 days for lamotrigine, 101 days for lithium, and 58 days for placebo. In secondary analyses, lithium was superior to placebo at delaying time to a

Table 2. Randomized Clinical Trials of Long-Term Antidepressant Treatment in Bipolar Disorders[a]

Study	Diagnosis (N)	Treatment	Duration (mo)	Outcome	Result
Prien et al, 1973[21]	BP-I (44)	Li vs IMI vs PBO	up to 24	Hospitalized or new treatment	Efficacy: Li > IMI = PBO in BP
Wehr and Goodwin, 1979[22]	BP-I (5)	Li vs Li + DMI	27 (mean)	Nurse ratings	Efficacy: Li + DMI > Li Switch & cycling rate: Li + DMI >> Li
Quitkin et al, 1981[20]	BP-I (75)	Li vs Li + IMI	19 (mean)	RDC episodes	Efficacy: Li = IMI Mania: IMI > Li (women)
Kane et al, 1982[23]	BP-II (27), UP (22)	Li vs IMI vs Li + IMI vs PBO	11 (mean)	RDC episodes	Efficacy: Li > PBO; IMI = PBO
Prien et al, 1984[24]	BP-I (117), UP (150)	Li vs Li + IMI vs IMI	up to 24	RDC episodes	Efficacy: Li = Li + IMI; IMI more mania
Sachs et al, 1994[25]	BP-I (15) (19 treatment trials)	BUP vs DMI	up to 12	DSM-III-R episodes	Efficacy: Li + BUP = Li + DMI Mania: DMI > BUP
Amsterdam et al, 1998[26]	BP-II (80), matched UP (79), unmatched UP controls (661)	FLX vs PBO	up to 14	DSM-III-R episodes	Efficacy: FLX similar in BP-II & UP Switch rate: BP > UP

[a]Reprinted with permission from Ghaemi et al.[17]
Abbreviations: BP = bipolar disorder (type I or II); BUP = bupropion; DMI = desipramine HCl; FLX = fluoxetine; IMI = imipramine HCl; Li = lithium carbonate; PBO = placebo; RDC = Research Diagnostic Criteria; UP = unipolar depression. Symbols: > = more effective than, >> = much more effective than. Efficacy results are for bipolar depressive symptoms or episodes unless stated otherwise.

manic, hypomanic, or mixed episode, whereas lamotrigine was superior to placebo in delaying time to a depressive episode. These secondary analyses, however, would not be statistically significant after the Bonferroni correction.

Another study[16] did not find lamotrigine monotherapy to be effective in the treatment of patients suffering from bipolar disorder with rapid cycling. A total of 324 patients, who were either euthymic or experiencing a mood episode, entered an open-label preliminary phase. This phase consisted of a 6-week titration period of lamotrigine to a target dose of 200 mg/day. All participants were 18 years or older with a DSM-IV diagnosis of bipolar I or II with rapid cycling. After 6 weeks, 182 patients were then randomly assigned to lamotrigine or placebo for a 26-week, double-blind treatment phase. The primary outcome measure was the time to additional pharmacotherapy for emerging symptoms. Secondary efficacy measures included time to premature discontinuation, the percentage of patients who relapsed after 6 months, and changes in the GAS and CGI-S scores. In the primary analysis, no difference was found between the lamotrigine- and placebo-treated groups in regard to time to additional pharmacotherapy. Among secondary analyses, some benefit was observed with lamotrigine in patients with type II bipolar disorder. As a secondary finding, however, this result is not definitive.

Antidepressants

Long-term treatment of bipolar disorder with antidepressants has to be considered in terms of the risk-benefit ratio. On the benefit side, adjunctive antidepressant treatment may improve current acute depression symptoms in the short-term. In the long-term, however, for prevention of future episodes, studies[17,20] suggest that antidepressants are ineffective.

On the risk side, there is some evidence[18,19] of potential risk of rapid cycling or cycle acceleration with antidepressant treatment. Rapid cycling appears to happen in about 20% to 25% of patients treated with tricyclic antidepressants (TCAs).[18] In the only available observational data[19] comparing newer antidepressants and older antidepressants, we found that rates of rapid cycling in bipolar disorder were found to be similar between TCAs and selective serotonin reuptake inhibitors (SSRIs).

Data[17,20] on antidepressants in the long-term treatment of bipolar disorder suggest lack of efficacy. A review of research[17,20–26] on the use for long-term treatment of bipolar disorder found 7 blinded controlled trials that showed antidepressant monotherapy or adjunctive treatment as ineffective (Table 2). For example, one study[20] randomly assigned 75 patients who met the Research Diagnostic Criteria (RDC) for bipolar disorder to either a lithium (300 mg/day) plus placebo group (N = 38) or a lithium (300 mg/day) plus imipramine (100 to 150 mg/day) group (N = 37). Patients were required to have experienced episodes of mania as well as major or minor depression, maintained euthymia for at least 6 weeks while receiving lithium treatment, be 18 to 65 years old, and have no coexisting medical illness. Outcome measures included type of relapse, time to relapse, and subsequent illness. Thirty-two percent (N = 12) of lithium-imipramine–treated patients and 24% (N = 9) of lithium-placebo–treated patients relapsed. The lithium-imipramine group tended to have more manic relapses and did not have fewer depressive relapses than the lithium-placebo group.

The question has been raised whether discontinuation of antidepressants produces increased risk of depressive relapse. In one observational study,[27] a total of 84 patients with bipolar disorder were prescribed an antidepressant as a cotherapy with a mood stabilizer. After 6 months, 43

patients discontinued the antidepressant treatment, while the other 41 patients continued the antidepressant treatment for another 6 months. A significantly shorter time to depressive relapse was found among patients in the discontinuation group when compared to patients in the continuation group. The discontinuation group also experienced a significantly shorter period of euthymia before relapse than the continuation group.

As with any observational study, the primary question that needs to be raised is whether there was a risk of confounding bias, how this risk was assessed, and what attempts were made to control or adjust for such potential confounding effects. In randomized studies[17,20] of sufficient size, confounding effects are removed by the randomized study design. However, in observational, nonrandomized studies such as this one,[27] possible confounding effects can only be assessed in 2 ways: stratification or regression analysis. In the case of stratification, a relevant variable, such as rapid cycling, would be chosen, and the risks of depressive relapse would be assessed only in those with rapid cycling and in those without rapid cycling. If there is no difference in the 2 groups, then one could infer that rapid cycling did not have a confounding effect. In regression analyses, one could include factors such as rapid cycling in mathematical models for regression analysis (in the case of survival data, Cox regression). This study did not examine any variables for potential confounding effects; even though a Cox proportional hazards regression was conducted, no potential confounding variables were included in the regression model. The major potential confounders of interest are clinical factors (rapid cycling status, number of previous episodes, other measures of severity of illness, age, and gender) and the general impact of "confounding by indication," which refers to the factors influencing the nonrandom decisions of clinicians at the beginning of the study. As a consequence of these limitations, one cannot be certain of the validity of the results of this observational study.

In contrast, we have been conducting a randomized study[28] in order to avoid many of these limitations. In this open-randomized design, patients who had responded to a mood stabilizer plus an antidepressant for acute bipolar depression were assigned to either discontinue (short-term group) or to continue (long-term group) their current antidepressant treatment following recovery for 2 months. The primary outcome was the total affective morbidity, defined as the absolute sum of the scaled manic and depressive symptoms followed on a clinical monitoring form (0 = no symptoms, 1–6 = subsyndromal mood episode, > 6 = syndromal mood episode). An interim analysis of the data at the halfway point of this 5-year study has been conducted. A repeated measures linear regression of overall affective morbidity suggests that the antidepressant discontinuation group had slightly less overall affective morbidity after adjusting for the potential confounders ($\beta = -0.40$, 95% CI = –2.21 to 1.42). Further, stratification by rapid cycling suggests that overall affective morbidity is decreased in both rapid cyclers and non–rapid cyclers. In contrast to the above observational study,[27] a Cox regression analysis suggests no increased risk of relapse with antidepressant discontinuation (hazard ratio [HR] = 1.21, 95% CI = 0.37 to 3.97) compared to antidepressant continuation.

PSYCHOTHERAPY

Unfortunately, medication efficacy frequently does not translate into functional recovery. Consequently, there is growing interest in the use of psychotherapy to enhance remission and functional status. In 13 randomized studies among 896 patients, increased remission rates and decreased relapse rates were found when medication was combined with psychotherapy.[3]

The types of psychotherapy used in bipolar maintenance are primarily psychoeducational and cognitive-behavioral psychotherapies, although research has been done with family-based[29] and interpersonal[30] therapies. Evidence from psychotherapy relapse prevention data demonstrates that some forms of psychotherapy may be better at preventing depressive recurrence[31,32] while others may be better at preventing manic recurrence.[33,34]

Cognitive-Behavioral Therapy

Studies have shown that cognitive-behavioral therapy (CBT) is effective in preventing bipolar depressive episodes but not manic episodes.[31,34] One possible reason is that cognitive strategies focus on identification of automatic thought process, challenging negative thought patterns and confronting barriers to treatment.

Scott[31] explored the efficacy of cognitive therapy among patients with bipolar disorder who were taking medication. Forty-two participants were randomly placed in either a cognitive therapy (CT) group or a 6-month waiting list control (WLC) group. All participants were over 18 years of age with a lifetime diagnosis of bipolar I or II disorder and had experienced 1 or more affective disorders in the last 2 years. Patients in the CT group were required to participate in a maximum of twenty-five 45-minute sessions for a period of 6 months, and both groups continued to receive any previously prescribed medications. The CT group showed greater improvements in symptoms and functioning as measured by the Beck Depression Inventory, Internal State Scale, and Global Assessment of Functioning than patients in the WLC group.

A small pilot study[32] compared the efficacy of CBT in bipolar and unipolar depressed patients. Eleven participants with bipolar disorder were matched to 11 participants with unipolar depression. All participants were

between the ages of 18 and 65 years, met the RDC for bipolar I or II disorder (depressed) or unipolar depression, and had a score > 14 on the 17-item HAM-D. Patients with bipolar depression were also treated with lithium or an anticonvulsant mood stabilizer. Participants completed an individual CBT course after an initial assessment and 20 weeks of CBT based on standard protocol with modified specific techniques for the bipolar patients. Bipolar patients showed a mean reduction on HAM-D score of over 50%, which was comparable to the reduction seen in patients with unipolar depression.

Psychoeducation

Psychoeducation may help patients to identify the early symptoms of relapse and seek treatment before relapse actually occurs. Studies[33,34] have found that psychoeducation is particularly beneficial in the reduction of manic symptoms. Psychoeducation may also improve the long-term outcomes in bipolar patients.

A recent study[33] of group psychoeducation was partially aimed at trying to improve insight in patients with bipolar disorder, and it showed efficacy in improving long-term outcome. A total of 120 patients were randomized into 2, single-blind, parallel groups (N = 60 each) for 20 weeks of treatment and 2 years of follow-up study.

In the treatment phase, all patients received usual psychiatric care with standard pharmacologic treatment. All patients were seen by 2 psychiatrists and were advised to go to the bipolar disorder program center whenever they felt any change in mood or experienced other problems. The psychiatrists were blinded to the nature of treatments the patients were receiving and whether they were receiving psychoeducation. The psychoeducation group was required to attend 21 psychoeducation programs, each for 90 minutes. These programs were aimed at improving illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and lifestyle regularity. The control group was required to attend 20 weekly intervention group meetings.

During the 20-week treatment phase, 36 (60%) of control group patients suffered a recurrence of symptoms while only 23 (38%) of experimental group patients suffered from recurrence of symptoms. At the end of the 2-year follow-up phase, a statistically significant difference in recurrence was seen between groups; 55 patients (92%) in the control group and 40 patients (67%) in the psychoeducation group had a recurrence of symptoms. After 24 months, the cumulative mean number of hospitalizations per patient was significantly lower in the psychoeducation group (30%) than the control group (78%). Also, the mean number of days of hospitalization per patient was lower for the psychoeducation group (4.75 days) than in the control group (14.83 days). The psychoeducation group had a significantly longer time to any recurrence of symptoms than the control group.

CONCLUSIONS

Lithium has the greatest quantity and quality of data to support its use as a maintenance treatment in bipolar disorder. Anticonvulsants, such as divalproex, and atypical antipsychotics, such as olanzapine, are also useful, especially among patients suffering from mania. Depressive relapse, however, is still a concern. Unfortunately, long-term antidepressant use does not appear to be a simple solution. Standard antidepressants appear to be ineffective at best and potentially harmful at worst. Lamotrigine may have some specific benefit for depressive symptoms. Polypharmacy, however, is often a common thread among bipolar disorder patients. Long-term monotherapy with mood stabilizers has been noted in less than one third of bipolar patients.[35] Thus, polypharmacy with mood stabilizers primarily, while using antidepressants infrequently, appears to be the most effective approach to treating bipolar disorder. Psychotherapies, primarily psychoeducational and cognitive-behavioral, have demonstrated promise in enhancing remission and functional status in patients with bipolar disorder.

Drug names: bupropion (Wellbutrin and others), divalproex (Depakote), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, lithium, bupropion, and lamotrigine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression; and divalproex is not approved for the maintenance treatment of bipolar disorder.

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