Long-Term Management Strategies to Achieve Optimal Function in Patients With Bipolar Disorder

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Functional impairment is a problem for people with bipolar disorder. Predictors of poor functional outcome are psychiatric and medical comorbidity, interepisode subsyndromal symptoms, psychosis during a manic or mixed episode, and low premorbid functioning. Cognitive dysfunction may also be a contributory factor in functional impairment. Several psychosocial interventions designed for people with bipolar disorder have demonstrated success in improving syndromal outcomes, but the effects of psychosocial interventions on functioning and cognition have not been examined. Among pharmacologic interventions available for long-term treatment of bipolar disorder, there is a strong clinical trend away from monotherapy and toward combination therapy. Lithium, lamotrigine, olanzapine, and aripiprazole have all shown substantial improvements in relapse rates compared with placebo. Although some of these medications show superior results compared with the others in preventing the recurrence of either depressive or manic episodes, only anecdotal evidence exists regarding their effect on cognition. Combination therapy with antipsychotics or antidepressants has also been shown to produce better syndromal outcomes in people with bipolar disorder, but inadequate evidence is available on cognitive outcomes. Substantial information is needed regarding the prevalence and causes of cognitive dysfunction in bipolar disorder, the effects of existing treatments on cognition, and long-term treatments to improve cognition and functioning.

(J Clin Psychiatry 2006;67[suppl 9]:19–24)

The goals of long-term pharmacologic and psychosocial strategies to treat bipolar disorder are to reduce symptoms and improve functional outcomes, but a relative dearth of literature is available concerning long-term management strategies to achieve optimal function. Improved relapse rates have been achieved with particular pharmacologic and psychosocial treatments for long-term management of bipolar disorder; however, interventions that address cognitive impairment and move the patient toward functional recovery hold promise for better functional outcomes. The prevalence and types of cognitive dysfunction in bipolar disorder, its causes, and the efficacy of various treatments available to improve cognition and hence achieve optimal function have not been well studied.

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This article was derived from the planning roundtable "Improving Cognitive Function and Functional Outcome in Severe Mental Illness," which was held January 13, 2006, in Dallas, Tex., and supported by an educational grant from Bristol-Myers Squibb Company.

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FUNCTIONAL OUTCOMES

Over the last 40 years or so, many outcome studies have examined the long-term course of illness in people with bipolar disorder. This article focuses on studies that examined functional outcome in people with bipolar illness.

Practitioners are now aware that the old medical school description of the course of illness in bipolar disorder in which people have discrete periods of mania and depression punctuated by sometimes prolonged periods of wellness is, unfortunately, nearly mythical and probably applies to a relatively small percentage of people with this illness. Zarate et al.[1] reviewed studies, dating from 1979 to 2000, that examined functional outcomes in bipolar disorder and that included a diverse range of sample sizes and duration of follow-up (Table 1).[2] Among the studies reviewed, those[3–8] that followed patients for a shorter period, from 6 months to 1 or 2 years, typically found high rates of functional impairment. Functional impairment was usually defined as an inability to, or protracted delay in, return to previous or premorbid level of functioning, such as getting back to work or school. Tohen and colleagues,[8] for example, found that by 2 years, 63% of patients who recovered syndromally did not achieve functional recovery. When studies[9–13] extended the duration of follow-up to 4 years or longer, the percentage of patients who had sub-

Table 1. Studies Reporting Functional Outcome in Bipolar Disorder[a]

Study	Participants (N)	Duration of Follow-Up (y)	Impaired (%)
Dion et al (1988)[3]	67	0.5	67
Keck et al (1998)[4]	134	1	76
O'Connell et al (1991)[5]	248	1	19
Strakowski et al (1998)[6]	109	1	65
Harrow et al (1990)[7]	73	1.7	34
Tohen et al (2000)[8]	219	2	63
Tohen et al (1990)[9]	75	4	28
Gitlin et al (1995)[10]	62	4.3	35
Goldberg et al (1995)[11]	51	4.6	22
Coryell et al (1993)[12]	29	5	31
Tsuang et al (1979)[13]	100	30	24

[a]Adapted with permission from Zarate et al.[1] and Goldberg and Harrow.[2]

stantial functional impairment tended to diminish, showing that with time many people with bipolar disorder ultimately regained functioning or learned to manage their illness more optimally. However, some patients are permanently disabled from this illness, despite aggressive pharmacologic and psychosocial treatment interventions.

Clinical Predictors of Functional Impairment

Clinicians and researchers have wondered why some patients with bipolar disorder have a worse course of illness that leads to long-term functional disability. Four clinical predictors of functional impairment have been identified fairly consistently across the body of literature.[4,10] The first is that the greater the degree of both psychiatric and medical comorbidity, the greater the extent, or likelihood, of poor functional outcome. Since bipolar disorder tends to be the psychiatric illness associated with the greatest degree of comorbidity,[14] many people with bipolar disorder have a poor functional outcome.

Secondly, the outcome study by Altshuler et al.[15] found interepisode or subsyndromal symptoms to be a powerful predictor of poor functional outcome, and this was especially true for persistent and pernicious depressive symptoms. Using the Hamilton Rating Scale for Depression (HAM-D) and the Global Assessment of Functioning (GAF) scale, 25 men with bipolar I disorder were evaluated for depressive symptoms and overall functioning. Scores on the GAF were significantly negatively correlated with HAM-D scores ($p = .001$), although none of the men had a HAM-D score high enough to be considered clinically depressed. These patients were not in full syndromal depressive episodes, but their illness had not been aggressively treated or had not responded sufficiently for the men to reach full remission of all affective symptoms, especially depressive symptoms.

Thirdly, work from Tohen et al.[8] and Strakowski and colleagues[6] showed that psychosis during a manic or mixed episode was a short-term predictor of poor functional outcome, and that was especially true over the first year or 2 following a hospitalization for a psychotic manic or mixed episode. However, in longer follow-up, out to 4 years, Tohen et al.[9] found that the ultimate prognosis was similar whether patients had nonpsychotic or psychotic, manic, or mixed episodes.

For a variety of reasons, including sociodemographic factors and support availability, low premorbid functioning was a fourth factor that tended to predict subsequent poor functioning.[6,9]

Cognitive Dysfunction

Few studies have systematically and carefully addressed cognitive function in the long-term outcome of people with bipolar illness, although naturalistic studies[16,17] have identified cognitive dysfunction as a persistent problem in a subgroup of people with bipolar illness. The issue of the confounding effects of treatments, however, has consistently been raised because many of our treatments of people with bipolar disorder have historically been associated with cognitive side effects. Lingering cognitive dysfunction in people with bipolar illness may be due to the illness, due to the treatment, or due to both.

Some investigators[18] have speculated that a subgroup of people with bipolar disorder who have enduring cognitive dysfunction may represent a different endophenotype of the illness. Identifying a presentation of bipolar disorder with a truly separate endophenotype would require a better ability to detect affected people early in the course of the illness and would probably also require specific targeted treatments directed at the cognitive dysfunction in those individuals. To my knowledge, no prospective treatment trials have evaluated an intervention of any kind targeted at improving cognitive dysfunction in people with bipolar disorder.

PSYCHOSOCIAL INTERVENTIONS

The psychosocial treatment of bipolar disorder was neglected until the last decade, but Otto and colleagues[19] reviewed several studies of different forms of psychosocial interventions specifically tailored for people with bipolar illness that examined the impact of these interventions on outcome. These included group and individual forms of psychotherapy as well as family therapy. Almost all these psychosocial interventions share some common features. First, they emphasize the need for medication, education about medications for bipolar illness, and overall adherence. Secondly, they emphasize detection of early warning signs for recurrence. Warning signs can be highly individual. Early detection and intervention are needed when evidence of manic, mixed, or depressive episodes presents. Thirdly, they stress the importance of helping patients cope with and anticipate stressors that trigger mood episodes and helping patients manage overall lifestyle.

For instance, emphasizing the need for a good night's sleep for people with bipolar illness is crucial because one of the most rapid ways of destabilizing the course of illness, even in someone with adequate treatment, is to deprive them of sleep. Fourthly, it is considered important to identify and treat co-occurring illnesses, especially alcohol and substance use, and comorbid conditions such as anxiety disorder. As mentioned earlier, the problem of persistent subsyndromal depressive symptoms needs to be addressed to make sure that people with those depressive symptoms are identified and the symptoms brought into remission. Manic, mixed, and depressive episodes can all, of course, also cause cognitive symptoms.

All the studies of randomized controlled trials of psychosocial interventions to manage bipolar disorder reviewed by Otto et al.[19] showed that cognitive-behavioral strategies led to measurable and relevant improvements in outcome. Group psychotherapy, individual targeted forms of psychotherapy, and family therapy all showed a reduction in hospitalizations and recurrence of mood episodes. Psychotherapy was especially effective in the prevention of depressive episodes and in the improvement in rates of treatment nonadherence.

There are few data from randomized, controlled trials on outcome measures that targeted functional improvement in people with bipolar disorder. To my knowledge, there have also been no randomized, controlled trials that systematically examined the effects of a treatment on cognitive outcome measures, especially in the long term. A huge unmet need exists for research into cognitive outcome measures that could dramatically and favorably impact the long-term course of people with bipolar disorder. Many of the cognitive-behavioral therapy interventions that have been developed for bipolar disorder may not be accessible to or have much impact on people who have cognitive deficits, whether from treatment or from the illness itself.

PHARMACOLOGIC INTERVENTIONS

Monotherapy

Four medications have been approved by the U.S. Food and Drug Administration (FDA) for maintenance treatment of bipolar disorder: lithium, lamotrigine, olanzapine, and aripiprazole. All these medications have been studied as long-term relapse prevention monotherapy in bipolar disorder, and the resulting data have implications for future study of cognitive improvement.

Lithium. An analysis[20] of placebo effect in maintenance treatment of bipolar disorder pooled results from 5 rigorous studies of lithium maintenance treatment and relapse rates in people with bipolar I disorder. This analysis showed that the protective effect of lithium is about 4-fold higher than placebo in relapse prevention, at both 6 months and 1 year.

Relapse rates for lithium have been compared with those for divalproex,[21] which is approved for use in acute mania or mixed episodes but not for maintenance treatment. This is a negative study, in that divalproex and lithium were not significantly superior to placebo in relapse prevention for any mood episode. This study has been fairly criticized[21,22] for some methodological issues that were not anticipated at the time. The criticism arose, in part, because about 40% of patients included in this study had never been hospitalized for a manic episode. The inclusion of these patients may have, in some ways, contributed to a higher-than-expected placebo response rate or lack of placebo relapse rate.

Lithium has also been compared to carbamazepine, another medication without FDA approval for maintenance treatment in bipolar disorder. All placebo-controlled trials of carbamazepine, to my knowledge, are confounded by adjunctive antimanic or antidepressant effects. The only rigorous, long-term maintenance study of carbamazepine was the European MAP (Multicenter Study of Long-Term Treatment of Affective and Schizoaffective Psychoses) study[23] that involved 144 patients with bipolar disorder in an open-label comparison trial between lithium and carbamazepine. The relapse rates at 2.5 years were high in both treatment groups (lithium 28%, carbamazepine 47%). However, lithium demonstrated a significant superiority over carbamazepine in 2 of the 4 outcome measures, one of which was a functional outcome measure.

Lamotrigine. The second drug to obtain FDA approval for maintenance treatment in bipolar disorder was lamotrigine. Two well-known lamotrigine studies[24,25] are the longest placebo-controlled trials of any agent in maintenance treatment of bipolar illness; both were 18-month studies. The elegance of these studies consists in their separating out acute mood episode prior to randomization, which is important because immediate prior episode in bipolar illness tends to predict risk of relapse into that subsequent mood episode. When patients come out of a depressive episode, their next mood episode is more likely to be a depressive episode than a manic episode, and vice versa. The results of these 2 studies were highly symmetrical. Both studies found that lamotrigine was superior to placebo in prevention of depressive episodes but not manic episodes, whereas in both trials lithium was found to be superior to placebo in prevention of manic episodes.

Anecdotal evidence suggests that lamotrigine has relatively few cognitive side effects, which is possibly an advantage, although this has yet to be demonstrated in rigorous trials. The results of these 2 studies[24,25] raise the question whether lithium and lamotrigine might be a particularly effective combination for maximizing prevention of both manic and depressive relapse, based on the selective benefits of each agent that were demonstrated.

Olanzapine. The third drug to obtain FDA approval for maintenance treatment was olanzapine. Two interesting

studies of olanzapine were carried out, one comparing it with lithium[26] and the other versus placebo.[27] The results of the olanzapine-lithium trial[26] indicated that olanzapine was superior to lithium in the prevention of manic recurrence and, therefore, had an impact on hospitalizations, since manic episodes tend to lead to hospitalization more than depressive episodes. No difference in relapse rates into depressive episodes was found between the olanzapine and the lithium groups.

Olanzapine's FDA approval was based on the placebo-controlled trial.[27] The overall rate of relapse in the olanzapine group was 46.7%, whereas the placebo group had a relapse rate of 80.1%. However, relapse rates parsed out into manic and depressive episodes show that olanzapine was associated with an especially lower rate of manic recurrence compared with placebo, having about a 4-fold greater protective effect, whereas only about a 2-fold greater protective effect was seen in depressive episodes.

Aripiprazole. The last of the agents that has FDA approval for maintenance treatment in bipolar disorder and for which there are placebo-controlled trial data is aripiprazole. The results of a 6-month trial[28] showed that aripiprazole was superior to placebo at 6 months in preventing overall relapses into manic and depressive episodes. The 6-month duration was chosen for ease of comparison with the early lithium data[20] that showed lithium's protective effects to be evident by 6 months. Aripiprazole showed an interesting separation in how well it prevented manic or depressive episodes. Its effects were most robust in preventing manic recurrence. Only about 10% of patients in the aripiprazole group had a manic episode over a 6-month period, compared with about 40% in the placebo group; whereas there was no significant difference in the protective effect of aripiprazole over placebo in depressive episodes. This result may be an artifact of trial design because, unlike the lamotrigine trials[24,25] in which 2 homogeneous groups of patients—one coming out of a bipolar depressive episode and one coming out of a bipolar manic episode—were randomized into maintenance treatment, subjects entering the aripiprazole study were coming out of a manic or a mixed episode and, therefore, were more likely to relapse into a manic episode rather than a depressive episode. The study may have been designed primarily to find out if there was a difference in favor of drug over placebo in prevention of manic rather than depressive recurrence, and that is what the results showed.

Anecdotally, along with lamotrigine, aripiprazole is regarded clinically as having a fairly favorable effect on cognition, and this drug, like lamotrigine, may be particularly suited to studies in which cognitive improvement is potentially demonstrated.

Combination Therapy

Combination treatment is the clinically preferred mode for people with bipolar disorder, but remarkably, this has been poorly studied.[29–31] Only 2 studies have investigated whether 2 medicines are better than 1 for people with bipolar illness. The first is Solomon and colleagues' small pilot study,[32] which included only 12 patients treated with lithium and either divalproex or placebo. The second is Tohen and colleagues' double-blind, placebo-controlled study[33] of 344 patients that examined whether people who responded to olanzapine with valproate or lithium should continue on that combination or return to outpatient monotherapy with valproate or lithium. In the study by Tohen et al.,[33] combination therapy was associated with a much better outcome than monotherapy, especially in relapse into manic episodes and in improvement in depressive episodes. Patients in the cotherapy group with moderate to severe symptoms of depression showed an almost 7-fold greater improvement on the HAM-D_{21} scale, and nearly 5 times as many of them showed at least a 50% improvement of depressive symptoms compared with the monotherapy group.

The tiny study by Solomon and colleagues[32] was the first combination therapy versus monotherapy study to show that combination therapy resulted in improved rates of relapse. Patients, followed for up to 1 year, treated with lithium and placebo had a 71% rate of recurrence, whereas the combination therapy group treated with lithium plus divalproex sodium had no recurrence.

No one has assessed whether combination therapy is associated with more cognitive side effects. Combination therapy with agents like lithium and divalproex, each of which could have highly specific cognitive side effects, could have a potential detrimental effect on at least that outcome measure.

Another kind of combination therapy is treatment with antidepressants in addition to mood stabilizers. The issue of treatment with antidepressants is highly relevant because they are among the most commonly prescribed class of drugs for bipolar disorder in the United States, and functional outcome is critically linked to depressive symptoms. Antidepressant use, especially for the long-term treatment of bipolar illness, still remains controversial because of the risk of precipitation of a manic, mixed, or hypomanic episode and because of the risk of producing rapid cycling.

Studies by Altshuler and colleagues,[34,35] one of which includes data from the Stanley Foundation Bipolar Network,[34] investigated whether patients who had a bipolar depressive episode and either stayed on an antidepressant or had that antidepressant tapered off showed a difference in risk of recurrence of depression and a difference in risk of precipitation of mania. Both of these studies are retrospective and naturalistic, with resultant limitations. The problem with naturalistic data is that they are not randomized and there may be a selection bias; patients who had frequent recurrent depressive episodes in the past may have been more willing to or more likely to have been

maintained on antidepressants and, therefore, may have selectively benefited from staying on those agents. Both studies showed that staying on the antidepressant typically was associated with a better outcome, especially a lower rate of recurrent depressive episodes, but without a significantly greater risk of switching into mania or cycling. In the 2003 study,[34] in 1 year, the rates of emergent depression were 36% for those treated with antidepressants versus 70% for those without. Those who discontinued antidepressant treatment within 6 months of attaining euthymia showed a shorter time before experiencing a manic episode than did people who continued to receive antidepressant treatment ($p = .04$). The 2001 study[35] showed that patients who continued antidepressant treatment for at least 6 months after achieving euthymia were significantly less likely to suffer depressive relapse than those who discontinued antidepressant treatment ($p = .02$).

UNMET NEEDS

Although several long-term management strategies are available to treat bipolar disorder and some pharmacologic treatments have shown greater efficacy in reducing relapse into either depressive or manic episodes, there is a lack of information concerning the effects of both psychosocial and pharmacologic interventions on cognition and the role of cognition in achieving optimal syndromal and functional outcomes in these patients. From this summary of data, the following 4 substantially unaddressed needs emerge related to determining the best long-term management strategies to achieve optimal function in patients with bipolar disorder. First, information is needed on the prevalence and specific types of cognitive dysfunction in people with bipolar disorder. We need to know to what extent cognitive dysfunction is due to the illness, due to the potential endophenotypic presentation of the illness, compounded by certain medications used to treat mood symptoms of bipolar disorder, or favorably influenced by specific medicines now in development or used for bipolar disorder. Second, information is required about the impact of cognitive dysfunction not only on symptomatic outcome but also on functional outcome of bipolar disorder. Third, it is necessary to understand the impacts of the pharmacologic and psychosocial interventions on cognitive measures, and whether there can, or should, be both psychosocial and pharmacologic interventions designed to work around or improve cognitive dysfunction in bipolar disorder. Lastly, an issue that pervades treatment of people with long-term, chronic mental illnesses is the need for identification of treatments to enhance specific cognitive deficits as they occur in people with bipolar illness.

Drug names: aripiprazole (Abilify), carbamazepine (Tegretol, Equetro, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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