Long-Term Treatment in Bipolar Disorder

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Bipolar disorder is a lifelong illness with a course that is usually chronic or recurrent. Severity of complications is generally proportionate to the number of episodes, especially depression. In addition to potentially preventing episodes, effective treatment reduces mortality. This article reviews long-term treatment strategies for bipolar disorder, focusing on depressive episodes, and discusses treatment studies, including problems in design. Treatment effectiveness, including reduction of suicide risk, is enhanced if patients and physicians collaboratively recognize and treat prodromal symptoms, preventing the emergence of episodes. Strategies for treatment differ as one progresses from obtaining syndromal recovery in the acute episode, to functional recovery during continuation treatment, to stability during maintenance treatment. Successful long-term treatment of bipolar disorder requires integrated pharmacologic and nonpharmacologic treatments combined with a therapeutic alliance that facilitates a proactive, preventive approach to the illness.

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COURSE OF ILLNESS AND NECESSITY FOR MAINTENANCE TREATMENTS

Bipolar disorder is a lifelong illness with a heterogeneous course.[1] Depression is usually the first, and most frequent, type of episode.[2] On average, people with bipolar disorder spend about 3 times as much time depressed as manic.[3] The personal, societal, and financial costs of the illness are substantial and depend largely on how many episodes a patient has,[4] especially depressive episodes.[5] Untreated patients are 2.5 times more likely to die in the next 12 months than individuals of the same sex and age without bipolar disorder.[6] This substantial mortality, from suicide and medical causes, is reduced by effective treatment.[6]

Frequent episodes of illness alter the response to acute treatment in subsequent episodes[7] and to maintenance treatment.[8] In fact, episodes seem to beget further episodes.[9] Because mood episodes have consequences that surpass their own duration, episode prevention is a primary goal of long-term treatment. However, patients may experience substantial impairment even in the absence of episodes.[10] Therefore, successful long-term treatment entails more than the prevention or amelioration of episodes.

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EVIDENCE FOR EFFECTIVE MAINTENANCE TREATMENTS

Treatments Supported by Evidence From Randomized Trials

Lithium,[11] lamotrigine,[12] and olanzapine[13] have been approved by the U.S. Food and Drug Administration for long-term treatment of bipolar disorder. Controlled trials also support other treatments, including divalproex in reducing incidence of depressive relapse[14] and certain atypical antipsychotic[15,16] drugs. Uncontrolled trials suggest that clozapine[17] and electroconvulsive treatment[18] are potentially effective in maintenance treatment when other agents are ineffective.

There is little evidence comparing treatments. In a placebo-controlled comparison[19] of lithium and divalproex, divalproex exceeded lithium in overall response and in prevention of depressive symptoms after an index manic episode. Another trial showed that lamotrigine, but not lithium, delayed relapse into depression, while lithium was more effective in delaying relapse into mania after either index manic[20] or depressive[21] episodes. The dropout rate with lamotrigine was substantially lower than that with lithium.[20,21] Olanzapine has been shown to prolong the time to any relapse compared with placebo in a group of subjects who had responded to acute treatment of manic episodes with open-label olanzapine.[22] Olanzapine was superior to lithium in delaying manic, but not depressive, relapse[23] and resembled divalproex in overall time to relapse after a manic episode.[24]

In nearly all published trials, most patients suffer relapse within 1 or 2 years even if given the active treatment in a positive trial, and a substantial minority of subjects who are randomly assigned to receive placebo do not suffer relapse.

Trial Limitations

Evidence for effectiveness of long-term treatments is affected by the nature of the index episode, nonrandom selection of participants based on early treatment response, rapid withdrawal of treatments, and use of mutually exclusive endpoints.[25,26] Most episodes of bipolar disorder are depressive, yet most continuation or maintenance trials have followed manic episodes. Despite the excellent critique of clinical trial strategies by Greenhouse et al.,[25] studies are still biased by relatively rapid dose reduction or discontinuation of an effective treatment in at least 1 therapeutic arm, predisposing subjects in that treatment arm to early relapse.[27,28] To my knowledge, no study has used the balanced initial and maintenance phase design proposed by these authors.[29]

Another potential source of bias is the use of enriched samples, where subjects must initially improve and/or remain stable for a specific duration with one of the randomized treatments before being randomly assigned to long-term treatment. This design may produce a nonrepresentative sample by selecting patients more likely to be responsive to the study drug. For example, the response to divalproex was substantially higher in subjects initially responding to it than in the subject group as a whole.[19] This enriched study design strategy has the advantage of mirroring clinical practice, since it is generally considered desirable to continue an initially successful treatment if it is safe and well tolerated,[28] and patients tend to do worse if an initially successful treatment is discontinued.[19,29] However, additional bias is introduced if 2 drugs are compared in a sample enriched for responders to one of them, as was the case in the comparisons of lamotrigine and lithium.[12] While overall response to lamotrigine and lithium appeared similar in these studies, the samples were enriched with respect to response to lamotrigine.

Subjects of controlled maintenance studies, especially if there is a placebo arm, may be less ill or have fewer complications than the general population of patients with bipolar disorder. Subjects with substantial risk for suicide or who have concomitant medical or psychiatric illnesses are generally excluded.[30] These considerations may explain why real-life outcome studies in bipolar disorder have often produced results less favorable than those of randomized trials.[31,32]

As in acute treatment studies, response to monotherapy does not appear optimal even when better than placebo. Combined treatments may therefore be indicated, though there is little evidence regarding response to treatment combinations. Addition of antidepressants appeared not to improve prevention of depressive episodes, though most studies used tricyclic antidepressants.[33] The combination of lithium and carbamazepine appeared better than either agent alone, but the combination was always given last.[34] The combination of olanzapine with lithium or divalproex was reported to be superior to lithium or divalproex alone.[13] However, this was actually a discontinuation study, since subjects had reached acute remission on the combination treatment before being randomly assigned to continue to receive olanzapine or to have it discontinued. The excess relapses in subjects who had olanzapine withdrawn all occurred in the first few weeks of randomization, consistent with a discontinuation effect. Therefore, this study does not address the question of whether addition of olanzapine as a maintenance treatment would improve response to lithium or to divalproex in general, or in patients not responding to one of these agents. It does, however, underscore the need to use caution in discontinuing any medicine that was required to achieve response in an acute episode.

Nonpharmacologic Treatments

Nonpharmacologic treatments are potentially valuable in treating bipolar disorder, but little controlled evidence supports such treatments. Nonpharmacologic treatments are potentially useful for comorbid conditions, such as substance abuse,[35] and for relapse prevention, by strategies such as protection of social rhythms.[36] Education of the patient and the family is vital to the long-term success of any treatment.[37]

PREVENTION OF DEPRESSIVE EPISODES

As mentioned earlier, despite the prominent role of depression in bipolar disorder, most maintenance data focus on preventing manic episodes in patients who were recently manic. This fact contributes to the difference between efficacy in clinical trials and real-life outcome.

Maintenance Treatments for Depression

Table 1 summarizes evidence for prevention or delay of depressive relapse in bipolar disorder, derived from published placebo-controlled studies. Lithium, the most-studied agent, was reported in some,[39,40] but not all,[38,39] early studies to reduce the rate of relapse into depression. In recent placebo-controlled studies,[19–21] lithium did not do so. One problem in the earlier studies was that, especially after index manic episodes, patients dropped out of the study during manic relapse before they had an opportunity to become depressed; more recent studies using time to the first intervention or episode as a primary endpoint had the same potential problem. Patient characteristics in the original studies differed from those in more recent studies, including less exposure to previous treatment.[39] A potential negative bias was produced by lack of adequate power in some studies.[38,39] In the lithium-lamotrigine studies, enrichment of the sample with lamotrigine responders, who were then able to remain stable for at least 2 weeks on lamotrigine monotherapy after resolution of the index episode, may have reduced the effect of lithium in preventing depression, although lithium effectively reduced relapse to mania in these subjects.[20,21] The valproate-lithium study

Table 1. Prevention of Depression in Bipolar Disorder (placebo-controlled studies)

Reference	Subjects (N, diagnosis)	Duration (mo)	Index Episode	Result (lithium)	Result (other)	Remarks
Dunner et al[38]	40, bipolar II	16	None	–	Not applicable	
Fieve et al[39]	35, bipolar I; 18, bipolar II	30	Depressed	+	Not applicable	Two thirds of patients had no previous lithium treatment
Prien et al[40]	205, bipolar I	24	Manic	–	Not applicable	Two thirds of episodes were manic
Prien et al[40]	44, bipolar II	24	Depressed	+	Not applicable	Two thirds of episodes were depressed
Bowden et al[19]	372, bipolar I	12	Manic	–	Divalproex +	Divalproex also increased response to adjunctive selective serotonin reuptake inhibitor
Bowden et al[20]	175, bipolar I	18	Manic	–	Lamotrigine +	
Calabrese et al[21]	463, bipolar I	18	Depressed	–	Lamotrigine +	

Symbols: + = positive, – = negative.

was more conservative, since it included subjects responding initially to either lithium or valproate in addition to other treatments.[19] Divalproex significantly reduced the proportion of subjects experiencing relapse into depression and was associated with greater effectiveness of adjunctive antidepressant treatment.[14] Olanzapine delayed depressive relapse in subjects initially responding to open-label treatment with the same drug. No other agent has been reported to reduce or delay depressive relapse in a placebo-controlled study.

Use of Antidepressants

The long-term use of antidepressants is potentially problematic in bipolar disorder. These agents appear effective in treatment of bipolar depressive episodes, although evidence is far less extensive than is that for treating nonbipolar depressions.[41] Short-term mood destabilization,[42] and early loss of response,[43] may characterize use of antidepressants in many patients, although the true prevalence of these problems is hard to determine. Potentially of more concern, antidepressants may cause long-term mood destabilization,[44] although, again, extensive, rigorous evidence is lacking.

As reviewed by Ghaemi et al.,[33] there is no evidence from placebo-controlled studies that addition of an antidepressant to a mood-stabilizing agent improves prophylaxis of depression in bipolar disorder, with at least 7 negative published studies. Two naturalistic studies[45,46] showed that, in patients who had experienced a robust response to an antidepressant added to a mood-stabilizing agent, those in whom the antidepressant was discontinued were more likely to relapse. The first was a retrospective study[45] in which 19 patients continuing lithium were compared with 25 patients who discontinued lithium. The second was a prospective study[46] of 84 subjects who achieved relapse from depression upon addition of an antidepressant, with outcome compared relative to whether the antidepressant was continued for at least 6 months. In both studies, there were no randomization of antidepressant use or discontinuation and no systematic information about reasons for discontinuation, so patients continuing the antidepressant may not have been clinically comparable to those for whom the antidepressant was discontinued. Further, the subjects with good antidepressant response were derived from a larger population. The results of these studies are consistent with observations by Ghaemi and Goodwin[47] that a subgroup of about 20% of subjects with bipolar disorder may require antidepressive treatments for optimum response and may benefit from continued treatment, at least for over 6 months. Therefore, the average patient with bipolar disorder may not benefit from long-term antidepressant treatment, but a subgroup probably does. This possibility needs to be demonstrated using a prospective, controlled study.

THE TRANSITION TO MAINTENANCE TREATMENT

Symptoms of acute manic episodes improve substantially over a few weeks of effective treatment. This relatively rapid symptomatic recovery is deceptive. Functional recovery, including return of adaptive, social, and occupational capabilities, is more likely to take months.[48] In some patients, functional recovery may never occur due to early relapse or chronic illness. During the period between symptomatic and functional recovery, patients are generally expected to return to their former obligations, and there is a substantial reduction in the intensity of treatment and observation. This potentially dangerous combination may contribute to the increased risk for suicide during the months following hospitalization.[49]

When symptoms initially improve, medicines are often tapered or discontinued, and normal life stressors are resumed. Due to continued functional impairment during this period, pharmacologic changes should be made cautiously, because patients need protection against overstimulation and relapse.[48] Initially, medicine should be adjusted based on tolerability and safety. More gradually, as the patient adapts to the normal living and occupational situation, medicines considered to be nonessential, such as adjunctive treatments, can be discontinued carefully over a period of months, with reinstitution of medicine or suspension of taper if problems arise.

The need for nonpharmacologic treatment changes as the patient passes from symptomatic to functional

Table 2. Treatment Strategies for Bipolar Disorder Based on Phase of Illness

Strategy	Phase		
	Acute	Continuation	Maintenance
Goal	Syndromal recovery	Functional recovery	Stability
Time	0–8 wk	1–12 mo	Indefinite
Treatment			
Pharmacologic	Maximize mood stabilizers, adjunctive treatments	Adjust for tolerability, begin taper of adjunctive treatments	Optimize, address prodromal symptoms
Nonpharmacologic	Structure, support, education of family	Behavioral treatments, systems measures, institute monitoring	Strategies to optimize adaptation, monitor for prodromal symptoms and other psychiatric, medical, or social changes

recovery,[37] as summarized in Table 2. During the acute episode, education for the family and provision of structure and support are the chief therapeutic modalities. During the transition between symptomatic and functional recovery, monitoring and educational measures can be instituted to prepare the patient for the maintenance period. Cognitive-behavioral and similar treatments can be instituted during this period. As the patient enters functional recovery, insight-oriented therapies can be instituted if they are appropriate for the patient.

STRATEGIES FOR MONITORING AND ANTICIPATING THE COURSE OF ILLNESS

Prodromes and the Time Course of Episodes

Depressive and manic episodes are preceded by a period, usually at least 1 or 2 weeks, during which goal-directed activity, the sleep-activity cycle, or a similar basic aspect of cognitive and affective function is abnormal.[50] The exact pattern varies considerably but tends to be consistent within the same individual. Therefore, it is valuable to identify a patient's prodromal pattern and to develop preventive strategies that can forestall an impending episode.[51] The development of such strategies has been shown to reduce rates of relapse.[52]

Collaborative monitoring facilitates the identification of prodromes and evaluation of treatments and helps the patient develop responsibility for his or her health.[53] Prospective charting of mood, sleep, and other aspects of illness by the patient can be a valuable element of treatment.[54]

Preventive Treatment During Pregnancy and Childbirth

Bipolar disorder spans the reproductive life span. Risk of relapse is not reduced during pregnancy and increases substantially after childbirth.[55] Lithium, valproate, and carbamazepine are associated with risk for developmental abnormalities.[56] It is important to use the minimum number of treatments possible at the lowest dose, with probable suspension of some treatments early in pregnancy. A strategy for careful treatment and monitoring must be developed, preferably well before the actual pregnancy.

Comprehensive reviews of treatment of bipolar disorder during pregnancy are available.[57] Folic acid supplements can reduce the incidence of neural tube defects regardless of pharmacologic treatment, but they cannot be assumed to eliminate the increased risk from anticonvulsants. Any medicine to be discontinued should be tapered slowly. Treatments can be reinstituted late in the first trimester if necessary.[55] Conventional antipsychotics and electroconvulsive therapy can be used for severe emergent symptoms.[58,59] Collaborative monitoring to anticipate prodromal symptoms is very important during this period.

Reducing Risk for Suicide

Individuals with bipolar disorder have a 20- to 30-fold increase in suicide mortality over others of the same age and sex.[6,60] Even with treatment, the incidence of suicide mortality appears to be about 5-fold greater in those with bipolar disorder. Severe suicidal behavior appears to be associated with combined depression and activation, so mixed states may be especially treacherous.[61] Suicide risk is increased if there is a history of substance abuse,[61] perhaps in part due to the increases in mixed states and impulsivity associated with substance abuse.[62] Most suicidal behavior occurs during or directly after depressive or mixed episodes.[49]

While risk for completed or attempted suicide appears to be reduced during treatment, there is little information about the specificity of this effect. There is extensive evidence that suicidal behavior is reduced during lithium treatment and increases when treatment is stopped. Several factors complicate the interpretation of this evidence. None of the studies of suicide and treatment in bipolar disorder involved randomized treatments or any prospective effort to assure comparable treatment populations. Characteristics associated with good response to lithium, and therefore with the likelihood of remaining on treatment with lithium, include lack of mixed episodes, relatively infrequent episodes, and lack of substance abuse.[8,63] These characteristics are also associated with reduced inherent risk for suicide.[64] Therefore, the studies tend to have a potential bias in favor of lithium since characteristics associated with high risk for suicide are also associated with relative lack of response to lithium, so patients remaining on lithium treatment may be those least likely

Table 3. Strategies to Reduce Suicide Risk in Bipolar Disorder

Aim	Pharmacologic	Nonpharmacologic
Prevent episodes	Mood-stabilizing treatment, judicious use of adjunctive treatments	Recognize and address prodromal symptoms, protect sleep/activity rhythm
Watch for emergence of mixed states during depression or mania	Additional mood-stabilizing treatment if necessary	Monitor
Address substance abuse	Question of maximizing mood-stabilizing treatments or using topiramate	Cognitive-behavioral treatments, 12-step groups that recognize importance of medicine
Reduce impulsivity	Mood-stabilizing treatments, judicious use of adjunctive treatments	Watch for and address factors that increase activation, overstimulation, or stress; protect sleep/activity rhythm
Reduce anxiety	Judicious use of mood-stabilizing and adjunctive treatments	Cognitive-behavioral therapies for comorbid anxiety disorders
Enhance adaptive skills	Not applicable	Monitor environmental and life changes, develop adaptive and problem-solving abilities, encourage development of support networks

to make severe suicide attempts. In naturalistic studies comparing 2 treatments, it is likely that patients given the treatments will differ clinically. A randomized study, such as one[65] recently comparing clozapine and olanzapine in schizophrenia, is necessary to resolve this question.

Table 3 summarizes strategies for reducing suicide risk. In general, these strategies are all part of optimal maintenance treatment. The incorporation of suicide prevention into routine maintenance treatment was recently described by Sachs et al.[66] These strategies emphasize the importance of combining effective pharmacologic treatment with a structured and supportive therapeutic milieu.[67]

CONCLUSIONS

Pharmacologic treatment that is effective for an acute episode is likely to be preferable treatment for continuation or maintenance treatment. Relatively nonspecific measures such as education and monitoring, and more specific measures such as cognitive-behavioral treatments, may also be indicated. The effectiveness of treatment can be enhanced by identifying and addressing prodromal symptoms of recurrences. Optimal treatment requires collaborative and proactive integration of pharmacologic and nonpharmacologic modalities.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), topiramate (Topamax).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of any phase of bipolar disorder; clozapine is not approved for the treatment of bipolar mania or for bipolar maintenance; divalproex is not approved for bipolar maintenance treatment; and lamotrigine, lithium, and olanzapine are not approved for the treatment of bipolar depression.

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