

An Ever-Increasing Pharmacopoeia for the Management of Patients With Bipolar Disorder

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Bipolar disorder is a recurrent and relapsing mood disorder characterized by cycles of depression and mania. This article addresses the treatment of patients with bipolar mania, which remains one of the most difficult challenges facing clinicians. Patients require safe and effective therapeutic approaches for acute episodes of mania and depression, as well as chronic prophylaxis against future episodes. Monotherapeutic approaches are rarely effective, and combination approaches are associated with an increased risk of adverse events. Lithium is the only agent currently approved for the treatment of both acute episodes of mania and maintenance therapy; however, it is associated with a relatively poor response rate, high relapse rate, and less-than-optimal side effect profile. Other recent approaches have included several anticonvulsant agents, as well as conventional and atypical antipsychotic agents. *(J Clin Psychiatry 2000;61[suppl 13]:19-25)*

Bipolar disorder is a cyclic, recurrent, and relapsing mood disorder characterized by cycles of depression and mania. Historically, the management of bipolar disorder in general, and mania in particular, focused on lithium monotherapy. Unfortunately, no monotherapy with any agent has been shown to be effective in achieving remission in bipolar disorder. The poor response and high relapse rates associated with lithium monotherapy, taken together with its high rate of adverse effects, have served as an impetus for researchers to evaluate the safety and efficacy of a variety of anticonvulsant and antipsychotic agents as primary or adjunctive treatments for the management of manic depressive illness. The anticonvulsant agent valproate has been approved for the treatment of acute mania; numerous other agents are currently under investigation. It is of paramount importance to recognize the current regulatory requirements for approval of novel agents for the treatment of mood disorders, including mania and depression. Specifically, superiority of monotherapy with the new agents versus placebo in randomized controlled trials is considered the minimal requirement for U.S. Food and Drug Administration (FDA) approval.

TRADITIONAL THERAPEUTIC APPROACHES: LITHIUM

Lithium was approved in the United States in 1970 for the management of acute mania and in 1974 for maintenance therapy; it is currently the only agent approved for maintenance therapy of manic depressive illness. Lithium is particularly effective for the acute management of classic, euphoric mania. Factors that predict good response to lithium include a family history of lithium response and/or mood disorders,¹ mild mania, and few previous episodes.² In contrast, patients with a greater severity of mania, rapid-cycling disorder, a history of numerous previous episodes of mania, or mixed-state/dysphoric mania are among those least likely to respond to lithium therapy, as are patients with schizophrenia, psychotic mania, or organic mania secondary to head injury. Lithium is also less effective among bipolar patients with comorbid substance abuse.³

Lithium is associated with a slow onset of action. Approximately 50% of all bipolar patients will initially respond to lithium^{4,5}; however, up to 55% of patients develop resistance to lithium after 3 years of treatment.⁶ It has been estimated that only 33% of patients receiving lithium monotherapy remain episode-free for 2 years.¹

Among the numerous formulations of lithium are lithium citrate, lithium carbonate, and controlled-release lithium. Lithium has a very narrow therapeutic window; patients who exceed their appropriate dose are at high risk of lithium toxicity. Routine plasma level monitoring is essential. Lithium carbonate is administered 2 or 3 times daily and is associated with a relatively unfavorable side effect profile, including significant gastrointestinal upset

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(nausea, vomiting, diarrhea), polyuria, polydipsia, neuromuscular toxicity, weight gain, cognitive impairment (particularly among the elderly), and tremor. Lithium therapy often exacerbates acne and may cause hair loss, edema, and hypothyroidism. Hypothyroidism frequently leads to the development of a goiter. Controlled-release forms of lithium are generally administered in single doses at night and may be associated with fewer side effects, although no controlled data are available to support this view. Lithium therapy must be individualized, i.e., the appropriate acute and maintenance dosages must be identified to provide maximal efficacy with minimal adverse effects, without inducing toxicity.

Lithium is relatively contraindicated in patients with impaired renal function, as it is completely excreted in urine (96%) and perspiration (4%). Lithium can cause bradycardia and is therefore also relatively contraindicated in patients who have recently had a myocardial infarction. Furthermore, lithium should be prescribed with extreme caution in patients with ulcerative colitis or Crohn's disease, and it can markedly worsen psoriasis. Controversy continues regarding whether lithium should be used during pregnancy. The effects of lithium on coordination minimize its use among patients with cerebellar disorders. It is recommended that patients receive baseline laboratory testing prior to initiating lithium therapy to rule out hypothyroidism, pregnancy, cardiac pathology, and renal disease, with follow-up testing every 6 to 12 months. Patients who ingest lithium in overdose (plasma levels greater than 3.5 $\mu\text{g/L}$) often require emergency hemodialysis.

ANTICONVULSANT AGENTS

Valproate

In response to the problems associated with lithium therapy, as well as for theoretical considerations associated with the sensitization theory of bipolar disorder, anticonvulsants have been assessed as potential mood stabilizers. Valproate is currently the only anticonvulsant with an FDA indication for the management of mania associated with bipolar disorder. It has been found effective in those patients nonresponsive to lithium, including patients with rapid-cycling patterns,⁷ and there is evidence that it is superior to lithium for patients with mixed or dysphoric mania, rapid-cycling bipolar disorder, or mania with mild depression.^{5,8,9} Valproate is also more effective for patients with comorbid substance abuse. Valproate may be administered in a loading dose of 20 to 30 mg/kg for rapid stabilization among patients with severe acute mania¹⁰⁻¹²; other options include administration in either divided doses of 250 to 500 mg b.i.d. or 1 nighttime dose to attain a plasma level of 50 to 120 $\mu\text{g/mL}$. Valproate can be used synergistically with lithium, carbamazepine, and atypical antipsychotics.

The side effect profile of valproate is generally more favorable than that of lithium. Valproate has been associated with weight gain and hair loss, as well as mild and transient tremor, sedation, and gastrointestinal upset. Rare but potentially serious reactions include hepatitis and pancreatitis^{13,14}; recent investigations had suggested an increased risk of polycystic ovary disease in patients with epilepsy,¹⁵⁻¹⁷ but Altshuler¹⁸ found no such relationship in patients with bipolar disorder.

Like many anticonvulsants, valproate is teratogenic, and therefore contraindicated in pregnancy. The effects of valproate in combination with lithium are additive, in terms of both efficacy and side effects, and can therefore result in significant weight gain, with marked carbohydrate craving, as well as significant tremor. Recommended laboratory analyses include baseline liver function and blood drug levels, with follow-up every 6 months unless the patient becomes symptomatic.

Carbamazepine

Carbamazepine is an anticonvulsant with mood-stabilizing properties that has been utilized for the acute treatment of mania in bipolar disorder.¹⁹ Although 19 controlled studies have demonstrated the acute antimanic efficacy of carbamazepine,²⁰ it is not approved for this use in the United States. Carbamazepine has been shown, in numerous double-blind and open-randomized studies, to have equal efficacy in the long-term prophylaxis of both manic and depressive episodes, either alone or in combination with lithium.²⁰

As is seen with lithium or valproate, approximately two thirds of patients with bipolar mania respond to carbamazepine, and it is believed that up to one third of refractory patients benefit from its antidepressant effects. Carbamazepine is similar to antipsychotics in its rapid onset of antimanic efficacy; as such, lack of clinical improvement within 1 week of treatment initiation is suggestive of the need for alternative approaches.²⁰

Carbamazepine is generally administered in divided doses of 200 mg b.i.d. or t.i.d., which are increased until the therapeutic plasma range of 8 to 12 $\mu\text{g/mL}$ is attained. Rapid titration of carbamazepine is associated with increased adverse events, including neurotoxicity (sedation, diplopia, and ataxia) and gastrointestinal distress. Carbamazepine use is associated with other significant side effects: adverse effects on the liver, including thrombocytopenia; effects on bone marrow; and dermatologic rashes, including the potentially severe Stevens-Johnson syndrome. Rare incidences of aplastic anemia have also been reported.²⁰ Hyponatremia, another possible side effect, can lead to mental status changes, especially in the elderly.

Carbamazepine induces the cytochrome P450 3A4 isoenzyme, which can decrease the therapeutic efficacy of other agents, including oral contraceptives. Because carbamazepine is teratogenic, the combination of carba-

mazepine and oral contraceptives can be a particularly dangerous combination for women of childbearing age. As with other anticonvulsant agents, carbamazepine is also associated with weight gain, drowsiness, dizziness, and diplopia. Carbamazepine induces its own metabolism (autoinduction), frequently requiring increases in the effective dose over time. Less than half of the patients who initiate treatment with this agent are still receiving the drug 1 year later, owing to lack of efficacy and/or intolerance to side effects.

Lamotrigine

Lamotrigine is an anticonvulsant that has been used to treat bipolar disorder, particularly bipolar depression and rapid cycling. In an add-on, open-label study of lamotrigine including 16 treatment-refractory patients with bipolar I or II disorder,²¹ 50% of patients were very much or much improved an average of 5 weeks after starting lamotrigine treatment. In a similar open study,²² 5 of 7 rapid-cycling patients achieved and maintained euthymic response after addition of lamotrigine. These authors also reported a series of 22 bipolar depressed patients, 16 of whom responded to lamotrigine add-on therapy within 4 weeks.²³ Calabrese et al.²⁴ reviewed 14 reports involving a total of 207 lamotrigine-treated patients; the reports suggested broad spectrum efficacy in the treatment of depressed, hypomanic, manic, and mixed phases of the disorder. Included in this review was a prospective open-label study²⁵ conducted in 75 patients with bipolar I or II disorder in which lamotrigine was used as adjunctive (N = 60) or monotherapy (N = 15) treatment for 1 year. The overall response rates were 68% and 84% for patients entering in the depressed and manic/hypomanic/mixed phases of the illness, respectively; post hoc analyses suggested equivalent response in rapid- and non-rapid-cycling variants.²⁶ In a double-blind, placebo-controlled study of lamotrigine monotherapy in bipolar I depression,²⁷ lamotrigine, 50 and 200 mg/day, demonstrated significant antidepressant efficacy on a variety of measures, including the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale, and was well tolerated. Recently, a large (N = 180), double-blind, prospective study of rapid-cycling patients²⁸ was completed in which significant differences were shown in favor of lamotrigine on a variety of measures, including the percentage of patients who were maintained in a euthymic state for 6 months of monotherapy treatment (lamotrigine, 41% vs. placebo, 26%). As with carbamazepine, a rare but important side effect associated with the use of lamotrigine is the development of Stevens-Johnson syndrome, a potentially fatal dermatologic syndrome.

Gabapentin

Gabapentin is an anticonvulsant currently being studied for the treatment of bipolar disorder. Benefits of gabapentin

include the ability to rapidly adjust the dosage, a high therapeutic index, and the absence of required laboratory monitoring.²⁹ Gabapentin does not appear to interact with other psychotropic agents and has minimal adverse effects. It is administered in doses of 300 to 2400 mg/day and is generally better tolerated than other anticonvulsant agents. Gabapentin has also been associated with improvement of antipsychotic-induced movement disorders among patients on maintenance antipsychotic drug therapy.³⁰

However, research has demonstrated little efficacy with gabapentin monotherapy in the treatment of bipolar disorder.³¹ Pilot open-label trials suggested that it may be useful as adjunctive therapy for the management of modest mania³²⁻³⁴ or bipolar depression.³⁵⁻³⁷ Open-label, adjunctive gabapentin was administered to 9 consecutive outpatients with bipolar I or II disorder who were refractory to standard mood stabilizers; 7 patients experienced a moderate or marked reduction in manic symptoms within 1 month of treatment initiation.³² In another open-label study involving 10 patients with mixed symptoms, decreases in HAM-D ($p < .05$) and Bech-Rafaelson Mania Rating Scale scores ($p < .01$) were reported during the first week of treatment and sustained throughout the month-long study duration.³⁶ Adjunctive gabapentin was found to significantly reduce depression ratings ($p < .0001$) among 21 patients diagnosed with bipolar I mixed episodes, in contrast to only minimal and statistically insignificant reductions in patients' mania scores.³⁸

Finally, results of an open-label study³⁸ suggested that gabapentin may be effective as an adjunctive agent in the maintenance phase of treatment among some treatment-refractory patients. Nevertheless, there is an absence of well-designed investigations on the efficacy of gabapentin monotherapy for bipolar disorder, and additional data are required for its use as an adjunctive therapy.³⁹

Topiramate

Topiramate is an anticonvulsant approved for the adjunctive treatment of epilepsy. However, unlike other anticonvulsants, topiramate has few pharmacokinetic interactions with other mood stabilizers, which facilitates its use as adjunctive therapy. It also has little effect on either the bone marrow or the heart. Additionally, topiramate is the only mood stabilizer associated with weight loss.^{40,41} Small open-label pilot studies suggest that at least 50% of a group of patients with a wide range of bipolar disorders who received topiramate experienced marked or moderate improvement. A retrospective chart review by Marcotte⁴² found that approximately 50% of patients with rapid-cycling bipolar disorder, bipolar I disorder, bipolar II disorder, and mixed bipolar disorder showed marked or moderate improvement with topiramate adjunctive therapy.

In another study,⁴³ 53 of 56 outpatients with various subtypes of bipolar disorder who were nonresponsive to lithium, carbamazepine, or valproate received topiramate

as adjunctive therapy; the remaining 3 patients received topiramate as monotherapy. Of the 22 patients who had manic symptoms at the initiation of topiramate therapy, 59% were rated as much or very much improved; only 1 patient was rated as much or very much worsened. In contrast, only 1 of the 5 initially depressed patients was much or very much improved, whereas the remaining 4 patients displayed minimal or no change.

A third trial involved 11 patients with acute mania; of the 9 patients who remained in the study, 3 experienced a decline of at least 50% in their Young Mania Rating Scale scores, and another 2 improved their scores between 25% and 50%.⁴⁴ The remaining 4 patients experienced no change. Topiramate is increasingly used as an adjunct, with a goal not only to improve efficacy, but also to reduce weight gain induced by other agents used to treat bipolar disorder.

CONVENTIONAL ANTIPSYCHOTIC AGENTS

Conventional antipsychotic agents, such as haloperidol and chlorpromazine, have clear efficacy in the short-term treatment of acute mania. Several reports document the efficacy of chlorpromazine and related agents in the treatment of acute mania. However, with the advent of atypical antipsychotic agents, the conventional ones are now generally considered unacceptable because of their propensity for severe dystonic reactions, including laryngospasm, and the neuroleptic malignant syndrome. These particular side effects are potentially life threatening. Typical antipsychotic agents also lower seizure threshold and can impair cognition. Unlike schizophrenic patients, bipolar disorder patients, perhaps because of the white matter changes that occur within their central nervous system,^{45,46} are uniquely susceptible to tardive dyskinesia, a well-known disabling side effect of conventional antipsychotic agents.⁴⁷

ATYPICAL ANTIPSYCHOTIC AGENTS

In contrast to conventional antipsychotic agents, atypical antipsychotic agents, including clozapine, risperidone, quetiapine, and olanzapine, do not generally produce tardive dyskinesia, acute extrapyramidal symptoms, or elevation of plasma prolactin levels. Research also suggests the newer atypical agents to be more effective and less costly than traditional antipsychotic agents.⁴⁸⁻⁵⁰

Clozapine

A long-term follow-up study⁵¹ originally involving nearly 200 patients diagnosed with either treatment-refractory bipolar disorder (manic or mixed) or schizoaffective disorder, bipolar type suggested that clozapine monotherapy is an effective mood stabilizer. Of the 17 patients successfully contacted 16 months after initiation

of clozapine therapy, 65% remained on clozapine monotherapy with no subsequent rehospitalization or affective episode. Similar studies involving treatment-refractory patients with bipolar or schizoaffective disorder found clozapine monotherapy⁵² or adjunctive therapy⁵³ to be effective in patients with schizoaffective or rapid-cycling bipolar disorder.

Although there is a general consensus that clozapine is effective in refractory mania and facilitates a faster amelioration of manic symptoms than chlorpromazine,⁵⁴ it is an expensive agent because it requires frequent and regular blood tests to monitor for granulocytopenia. The increased risk of seizures associated with clozapine therapy, particularly at higher doses, may be offset by the adjunctive prescribing of an anticonvulsant agent also helpful in the treatment of bipolar disorder. In addition, clozapine has been shown to produce significant weight gain and sialorrhea, as well as significant anticholinergic effects.

Risperidone

Risperidone is an atypical antipsychotic that, unlike clozapine and olanzapine, is not associated with significant body weight gain. The initial studies conducted with risperidone used a wide dose range, with the higher doses associated with the development of extrapyramidal symptoms. Subsequent studies have found that lower doses (0.1-2 mg in adults; 2-4 mg in young adults) are well tolerated, with a low incidence of extrapyramidal side effects and presumably tardive dyskinesia.

One study found that two thirds of 13 patients who received adjunctive risperidone (1-6 mg) experienced improvement.⁵⁵ An open-label study involved the addition of risperidone to the current medication regimen of 12 outpatients diagnosed with bipolar type I disorder who had "breakthrough episodes" of mood disorder.⁵⁵ Four of the 8 patients who continued with the treatment experienced a 10- to 25-point improvement in Global Assessment of Functioning scores, and no patient experienced a worsening of mania.

Finally, controversy remains concerning the potential for risperidone to induce mania.⁵⁶⁻⁵⁹ It now appears likely that this is not the case. Nevertheless, this possibility is minimized when risperidone is administered in conjunction with a mood stabilizer.

Olanzapine

The FDA recently approved olanzapine for the treatment of acute manic episodes associated with bipolar disorder, on the basis of 2 placebo-controlled trials. A 3-week trial compared the safety and efficacy of olanzapine (10 mg once daily) with placebo in the treatment of 139 patients with acute mania; olanzapine had superior efficacy over placebo,⁶⁰ as it did in a 4-week trial involving 115 patients.⁶¹ The most common adverse effects associ-

ated with olanzapine included somnolence, dizziness, dry mouth, and weight gain.⁶¹

Olanzapine has a very low incidence of extrapyramidal symptoms, including tardive dyskinesia. However, as with risperidone, there are several reports of the induction of mania.⁶²⁻⁶⁴ There is also evidence linking cases of new-onset diabetes mellitus and diabetic ketoacidosis with the use of olanzapine.⁶⁵⁻⁶⁷ In addition, the weight gain associated with both clozapine and olanzapine is significantly increased when these atypical antipsychotic agents are combined with lithium or valproate.

NONPHARMACOLOGIC ADVANCES IN THE MANAGEMENT OF BIPOLAR DISORDER

Recent advances in the treatment of bipolar depression include the use of rapid-rate transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT). Initial investigations identified rTMS as a safe, noninvasive treatment for depression⁶⁸; rTMS has also been shown to evoke short-duration reversible episodes of hypomania among healthy volunteers.⁶⁹ Rapid-rate transcranial magnetic stimulation has been found to be therapeutic in the treatment of euphoric mania⁷⁰ and depression.⁷¹ Slow magnetic stimulation of the prefrontal cortex has also been shown to improve depressed mood in patients diagnosed with depression or schizophrenia.⁷² Further, while ECT has been shown to be efficacious in the treatment of both bipolar depression and mania, it appears to be most effective among patients with pure bipolar depression or pure bipolar mania and less effective among patients with mixed affective states.⁷³

BIPOLAR DEPRESSION

The mood disorders, including depression and bipolar disorder, are among the most common psychiatric conditions associated with suicide.⁷⁴ Between 25% and 50% of patients with bipolar disorder attempt suicide at least once. Currently, the most effective treatment against suicide remains lithium.⁷⁴ Patients with bipolar depression are frequently coadministered an antidepressant with lithium or valproate; the addition of an antidepressant appears to have greater efficacy than the addition of a second mood stabilizer.⁷⁵ Finally, preliminary studies suggest that lamotrigine may be effective in the management of bipolar depression⁷⁶ without causing mood destabilization.

CONCLUSIONS

The past decade has seen a plethora of research regarding the identification of safe and effective alternatives to lithium for the management of bipolar disorder. Although lithium remains the agent most often initially prescribed in mania, as well as the only FDA-approved agent for main-

tenance therapy, it is associated with relatively low response rates and compliance, high relapse rates, and significant adverse effects. Two agents, valproate and olanzapine, have received approval for the management of acute mania associated with bipolar disorder.

Few patients are treated long term with monotherapy with a mood stabilizer. The cyclic nature of this disorder almost always requires a polytherapeutic approach. Current investigations have predominantly focused on adjunctive therapies combining lithium or valproate with traditional and novel anticonvulsant agents, conventional antipsychotics, or atypical antipsychotic agents. The benefits of these respective adjunctive therapies must be balanced against the potentially significant side effects associated with combination therapies, including weight gain, tremor, and gastrointestinal and neurologic side effects. Topiramate is the only anticonvulsant or antipsychotic agent associated with weight loss. Finally, as compared with conventional antipsychotics, atypical antipsychotic agents are associated with minimal tardive dyskinesia and extrapyramidal symptoms, and appear to have antidepressant and antimanic properties.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax).

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