

Decision Tree for the Treatment of Bipolar Disorder

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Clinicians managing patients with bipolar disorder confront a myriad of complex treatment decisions. This complexity limits the practicality of treatment guidelines, which attempt to be comprehensive. A user-friendly guide can, however, be constructed by considering only the most common early critical decision points likely to be encountered in the management of bipolar patients: new onset of an acute manic or mixed episode, interepisode treatment entry, and initial treatment for acute bipolar depression. Three general treatment principles, i.e., use proven treatments first, use a mood stabilizer in every phase of the illness, and use a multiphase treatment strategy to link current assessment with an appropriate treatment plan, can be applied to guide decision making at critical decision points that follow entry into clinical care. To guide the selection of appropriate therapeutic agents, a simple grading system can be used to evaluate the weight of evidence supporting use of various options. Multiple high-quality studies with positive results support the use of lithium, divalproex, carbamazepine, olanzapine, and haloperidol as initial intervention for acute mania; other agents with positive results in one double-blind mania trial are reasonable first-line alternatives. In the absence of high-quality evidence to guide treatment selection for nonacutely ill bipolar patients, guidelines recommend maintenance mood-stabilizer treatment. Standard antidepressant medications do not appear to add statistically significant benefit beyond that of mood stabilizers alone; lithium and lamotrigine have shown some benefit, and promising preliminary data have been presented on the antidepressant benefit of divalproex and topiramate as well.

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Bipolar disorder presents a challenge for even the most experienced clinicians. Inherent variability of symptoms, high rates of substance abuse, medical comorbidity, a substantial risk of suicide, and other potentially severe adverse outcomes are among the characteristics that complicate clinical management of patients with bipolar disorder. The desire for guidance created by this apparent chaos spawns many laudable scholarly efforts to construct treatment algorithms and guidelines. Attempts to construct comprehensive algorithms, however, frequently prove counterproductive simply because those guidelines that approach the complexity required quickly render a densely detailed algorithm unsuitable for use by the practicing clinician. This article attempts to aid the clinical process by offering a simple decision tree (Figure 1).

How can the daunting complexity encountered in long-term management of bipolar disorder be incorporated into

a decision tree? Addressing only the most common initial branch points allows the construction of a user-friendly schematic decision tree. These branch points in the schema will be referred to as *early critical decision points*.

WHAT ARE THE MOST COMMON EARLY CRITICAL DECISION POINTS?

Logically, the most common early critical decision points reflect the entry points for bipolar patients seeking treatment. The most obvious entry point is the new onset of an acute manic or mixed episode. For previously undiagnosed patients or those currently untreated with known bipolar illness, a newly diagnosed manic episode requires the immediate choice of initial antimanic therapy. Another common entry point occurs at times after an acute episode when previously undiagnosed or untreated patients present to the clinician for other reasons. Treatment entry following diagnosis at an interepisode point might relate to the consequences of bipolar illness such as divorce, family discord, job loss, financial distress, and other legal difficulties or to common comorbid conditions such as abuse of psychoactive substances, panic, posttraumatic stress disorder, attention deficit disorder, or presumed personality disorders. When the assessment reveals the history of a prior hypomanic, manic, or mixed episode, the lifetime diagnosis of bipolar disorder is made. At that

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time, doctor and patient typically select an initial mood-stabilizer treatment in the absence of a current acute episode. The third common entry point involves treatment of depressive episodes. Choice of an initial antidepressant for episodes of bipolar depression is also often made in the context of a prior untreated episode of mood elevation as well as when the clinician faces a breakthrough episode of depression. This article will therefore consider these 3 early decision points.

GENERAL PRINCIPLES FOR SELECTION OF TREATMENT STRATEGIES

Three principles derived from the Expert Consensus Guidelines¹ can be applied to construct a “menu of reasonable choices” at each of the critical decision points:

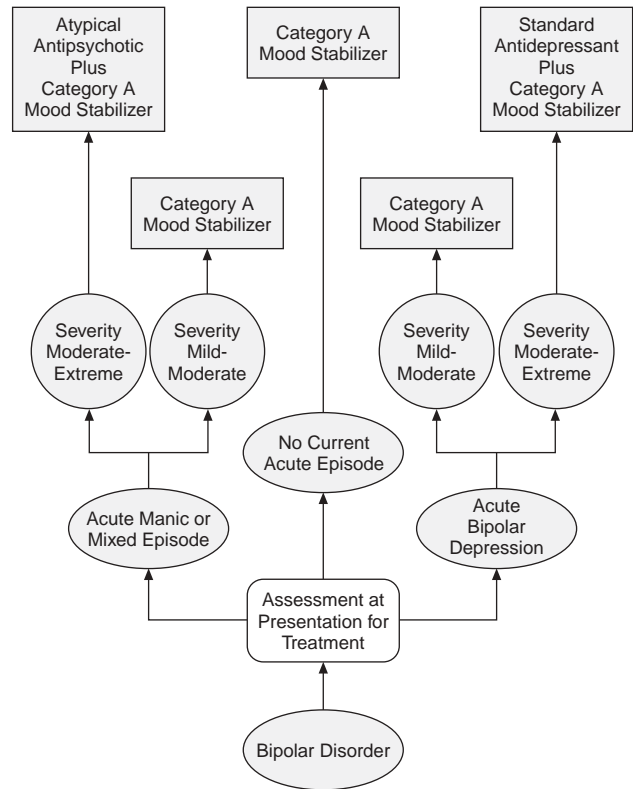
1. Use proven treatments first.
2. Use a mood stabilizer in every phase of the illness.
3. Use a multiphase treatment strategy to link current assessment with a treatment plan.

Using proven treatments first requires knowledge of the state of ever changing literature and some critical evaluation of the available evidence. It is worth noting that the seeming distinction between an “evidence-based approach” and “opinion-based surveys” is often difficult to find. This is not surprising since the available data do not speak for themselves. Interpretation always introduces opinion, not the least of which involves consideration of which data might actually generalize to the clinical question at hand. Surveys of expert opinion tend to reflect opinions formed in large measure by an awareness of evidence. Conversely, authors of evidence-based guidelines must interpret and extrapolate from available data and so render opinions reflecting their judgment. A simple grading system like that frequently employed in the construction of evidence-based guidelines can also be utilized to inform the critical analysis needed to construct a decision tree.²⁻⁵

WEIGHING THE EVIDENCE

The best quality of evidence comes from placebo-controlled double-blind trials in which treatment assignment is made by randomization. This level of evidence merits an “A” rating when the trial has included an appropriate sample sufficiently large to have at least an 80% chance of detecting a difference (statistical power) and provide confidence that the results are not due to chance alone. A detailed review of statistical considerations is beyond the scope of this article, but 2 points are important to note here. First, generally accepted statistical conventions allow the interpretation of results as significantly different when the probability that the observed difference is attributable to chance alone is 5% or less. Second, studies reporting differences insufficient to meet this standard

Figure 1. Decision Tree for Bipolar Disorder



merely fail to allow rejection of the null hypothesis and do not indicate that the conditions are the same. In other words, failure to detect a statistically significant difference does not mean treatment conditions are equivalent.

For purposes of weighing evidence for a decision tree, an “A+” might be reserved for those instances when fewer than 40 studies have been reported and more than one double-blind placebo-controlled study supports the same finding. An “A-” would indicate positive outcomes on some but not all relevant measures. Double-blind controlled trials without placebo or not completely satisfying the requirements above would be grade “B.” Open trials can be valuable when controlled and are most informative when the treatments being compared are assigned by randomization. Such trials will be graded “C” and “C+,” respectively. Uncontrolled observations are frequently problematic, but case series and even single case reports can provide a rationale for selecting treatment and can be graded “D” and “D-,” respectively (Table 1⁶⁻³⁹).

INITIAL INTERVENTION FOR ACUTE MANIA AND MIXED EPISODES

After diagnosis of a manic or mixed episode, the first critical decision point is the initiation of treatment to re-

Table 1. The Quality of Evidence^a

A Double-blind placebo-controlled trials with adequate samples
 B Double-blind comparator studies with adequate samples
 C Open trials with adequate samples
 D Uncontrolled observation or controlled study with ambiguous result
 E No published evidence
 F Available evidence negative

	Acute Mania/Mixed	Mood Stabilizer Prophylaxis	Acute Bipolar Depression
Lithium	A+	A+	A
Divalproex	A+	A-	D
Carbamazepine	A	B-	D
Lamotrigine	F	A+	A
Gabapentin	F	E	D
Topiramate	D	E	D
Aripiprazole	A	E	E
Haloperidol	A	E	E
Olanzapine	A+	E	A
Risperidone	A	E	D
Quetiapine	A	E	E
Ziprasidone	A	E	E
Omega-3	E	D	E

^aBased on references 6–39. A+ is reserved for those instances when fewer than 40 studies have been reported and more than one double-blind placebo-controlled study supports the same finding. A- indicates positive outcomes on some but not all relevant measures.

store behavioral control. Substances with mood-elevating effects should be tapered as quickly as clinical prudence permits. This includes standard antidepressant medications as well as stimulants, steroids, bronchodilators, decongestants, and substances of abuse.

The treatments with category A evidence could all be considered first-line options. In the United States, however, only lithium, divalproex, and olanzapine have U.S. Food and Drug Administration (FDA) approval for treatment of acute mania. Carbamazepine and antipsychotics such as risperidone, haloperidol, ziprasidone, aripiprazole, and quetiapine also have category A evidence and present reasonable alternative first-line treatments. Topiramate was found more efficacious than placebo on a global measure of severity.^{26,40} The advantage for topiramate on the mania rating scale designated as the primary outcome measure became statistically significant only in a post hoc analysis that removed subjects who discontinued a standard antidepressant at the time of study entry. Despite the differences in presumed mechanisms of drug action, the magnitude of antimanic efficacy across placebo-controlled mania studies is remarkably similar.^{41–44}

In a direct comparison of placebo, divalproex, and lithium, Bowden et al.⁴¹ found the advantage over placebo similar for lithium and divalproex. Two head-to-head comparisons between olanzapine and divalproex have been presented. Tohen et al.³² found a slight statistically significant advantage for olanzapine in nonpsychotic patients, but no advantage in psychotic mania. Zajecka et al.⁴⁵ reported on a study designed with sufficient statistical power to detect adverse effect differences only, but no-

tably found virtually identical efficacy for olanzapine and divalproex. Monotherapy with any of the agents supported by category A evidence is clearly more efficacious than placebo, but the average improvement observable over 3 weeks in an acute mania trial leaves patients with a manic syndrome in the mild-to-moderate range of severity.

It is natural to consider whether a polypharmacy approach might offer at least additive benefits beyond that offered by effective agents used as monotherapy, and whether the benefits of polypharmacy are negated by incremental increases in adverse effects. Controlled data are available for relatively few of the many possible combination treatment regimens. Pande et al.⁴⁶ reported no benefit for gabapentin (category F evidence) as an adjunct to acute treatment with lithium and/or divalproex. Category A evidence is, however, available from placebo-controlled studies that employed an add-on design. A trial in which lamotrigine or placebo was added to lithium found no benefit for acute mania.⁴⁷ Muller-Oerlinghausen et al.⁴⁸ found addition of valproate superior to placebo added on to an antipsychotic. In a 3-arm parallel-group study that compared mood stabilizer (lithium or valproate) plus placebo, mood stabilizer plus risperidone, and mood stabilizer plus haloperidol, Sachs et al.⁴³ found a rapid and robust benefit of combination treatment with antipsychotic medications. Combination treatment with risperidone was well tolerated and was associated with a significantly lower dropout rate than mood stabilizer alone. Tohen et al.⁴⁹ found the addition of olanzapine more effective than placebo for patients who remained at least moderately manic after 2 weeks of treatment with lithium or valproate. DelBello et al.⁵⁰ found similar antimanic benefit for quetiapine over placebo added to mood stabilizers in adolescent subjects.

While the evidence favoring combination of antipsychotics and a mood stabilizer is very consistent, the evidence from studies of combination treatment usually groups previously untreated patients with those who could be considered nonresponders to the nonstudy medication (mood stabilizer or antipsychotic) in use at study entry. Therefore the evidence for combining mood stabilizers and antipsychotics is strongest for patients presenting acutely manic despite receiving one of these treatments. Nonetheless, the tolerability of this combination treatment is also consistently excellent compared with monotherapy and favors use of antipsychotics with mood stabilizers in situations of high symptom acuity.

Although acute mania typically requires hospitalization, the acuity of symptoms at presentation varies widely. If agitation, violence, or psychosis is present, most guidelines favor use of an antipsychotic medication.^{1,3}

Placebo-controlled studies submitted for regulatory approval have demonstrated the benefit of monotherapy with carbamazepine, divalproex, lithium, and olanzapine for acute mania. While the statistical advantages of these treatments are not in doubt, clinical imperatives often re-

sult in the administration of combination treatment for acute mania and mixed episodes.

INITIAL TREATMENT IN THE ABSENCE OF A CURRENT ACUTE MANIC OR MIXED EPISODE: ENTRY SECONDARY TO DIAGNOSIS AT AN INTEREPISODE

Initiation of mood-stabilizer treatment for euthymic patients with a clear history of a manic or mixed episode targets prophylaxis. Who is a candidate for prophylactic mood-stabilizer treatment and what should the treatment be? Unfortunately, psychiatry must address these issues based on clinical logic and speculative extrapolation from samples only distantly related to those from which scientific evidence exists. Extrapolation of published data on prophylactic efficacy to this group must be regarded as highly speculative. The benefit of prophylactic maintenance treatment has been demonstrated in studies with design features that reduce the applicability of their findings to this decision point. Successful maintenance studies employ eligibility criteria that enrich the sample randomized with likely treatment responders. This describes the design of studies that limit enrollment to only patients who were prospectively rated responders during an open acute treatment phase just prior to randomization or who have prolonged periods of remission prior to study entry. Therefore, results from a maintenance study utilizing an enriched design do not generalize beyond the groups eligible for the study, e.g., known treatment responders.

Given the absence of data directly relevant to the population who actually enter treatment unmedicated and euthymic, what is a reasonable approach to treatment? Clinicians looking for evidence-based guidance have, unfortunately, no better evidence than that available in published maintenance studies. Following the basic principles above leads to the initial prescription of a mood stabilizer with proven evidence of efficacy. Since these patients begin treatment well, initial selection may be guided by the tolerability profile of the category A options.

While the quantity of data supporting maintenance treatment is greatest for lithium, nearly all of these studies used designs in which the placebo-treated groups abruptly discontinued ongoing lithium therapy. Consequently, the data from these studies overstate the likely benefit of lithium maintenance treatment beyond even that expected due to the enriched design. In the one published placebo-controlled parallel-group maintenance treatment study, Bowden et al.¹⁶ found evidence for the efficacy of divalproex (category A-) but not lithium over placebo.

Although there are a few reports of benefit of combining 2 or even 3 mood-stabilizing treatments for prophylaxis, none is adequately powered and sufficiently controlled (category D) to allow confident interpretation. In a small study that accepted patients in all phases of illness,

Stoll et al.³⁹ found an apparent statistically significant result for adjunctive treatment with omega-3 fatty acid. This evidence must be regarded as category D because the sample size was inadequate, the follow-up was limited to 4 months, and prophylactic utility cannot be judged without patients meeting criteria being in a well state. Omega-3 fatty acids might, however, be offered as an alternative treatment for patients who have been well in the absence of treatment for more than 5 years since their last acute episode. In a randomized open trial, Suppes et al.⁵¹ found long-term benefit of adjunctive clozapine (category C) over the clinician's choice of an alternative adjunctive treatment. Clozapine, however, is regarded as an option appropriate for refractory patients, not those at an early critical decision point. Prien and colleagues⁵² found no prophylactic advantage for combined lithium and imipramine over lithium alone and reported a particularly unfavorable outcome for patients randomized to maintenance treatment with imipramine monotherapy.

INITIAL TREATMENT FOR A CURRENT ACUTE DEPRESSIVE EPISODE IN PATIENTS WITH A PRIOR HISTORY OF MANIA

Several circumstances in which unmedicated bipolar patients seek treatment for depression are common. As described above for euthymic patients, taking a history from a depressed patient frequently reveals a prior manic episode that may or may not have been treated.^{53,54}

Even when the prior episode was treated, bipolar patients discontinue their medications frequently, and many enjoy a well interval that can last months or years. Therefore, it is fairly common to see previously diagnosed but currently unmedicated bipolar patients seeking treatment of a new depressive episode. Since principles 1, 2, and 3 above suggest all bipolar patients be offered a category A mood stabilizer, the larger question relates to the use of standard antidepressant medications. Most guidelines consider monotherapy with antidepressants to be contraindicated,^{1,3} reflecting concern about the risk of treatment-emergent switch to (hypo)mania. For bipolar depression of mild-to-moderate severity, some guidelines suggest it would be appropriate to initiate treatment with a category A mood stabilizer alone and reserve standard antidepressant for adjunctive use in nonresponders.

Despite the relatively large number of reports indicating that lithium's antidepressant properties were superior to placebo for bipolar depression, there remain few data comparing lithium or other mood stabilizers with standard antidepressants. In the only controlled double-blind study comparing standard antidepressants versus placebo medications as adjuncts to mood stabilizers, Nemeroff et al.¹⁴ compared adding placebo, imipramine, or paroxetine for patients, all of whom were also treated with lithium and had serum lithium levels above 0.5 mmol/L. Overall, this

study found the benefit of adjunctive standard antidepressants to be no better than that of lithium alone. A post hoc analysis did, however, find a benefit for the standard antidepressants in the subsample with serum lithium levels below 0.8 mmol/L.

Other mood stabilizers may have antidepressant efficacy similar to that of lithium. Sachs et al.⁵⁵ reported a small double-blind pilot study in which trends favoring divalproex over placebo as monotherapy for bipolar depression reached statistical significance at several timepoints. Though the divalproex response rate (43%) was not statistically superior to that observed for placebo (27%) in this study, it appears to be of similar efficacy as monotherapy to that reported by Kupfer et al.⁵⁶ for citalopram (47%) in an open uncontrolled add-on study. In a small study comparing bupropion versus topiramate as adjunctive treatment for bipolar depression, McIntyre et al.⁵⁷ found no differences in either efficacy or switch rates. Though promising, in the absence of a placebo control, a study finding of no difference is rendered ambiguous (category D).

CONCLUSION

Ample clear category A+ evidence supports initial intervention with lithium, divalproex, carbamazepine, olanzapine, and haloperidol for acute mania. Other antipsychotic medications with positive results in at least 1 double-blind mania trial are also reasonable first-line alternatives. Although many bipolar patients appear to benefit from acute and long-term combination treatment, current evidence supports combination treatment with antipsychotic medications and mood stabilizers for the acute phase of mania.

High quality evidence to guide selection of initial treatment for nonacutely ill bipolar patients is lacking. Guidelines suggest such patients should be offered treatment with mood-stabilizing medications. Further study is needed to clarify the benefit of atypical antipsychotics and other putative mood stabilizers for long-term treatment.

Standard antidepressants appear to be effective acutely, but as yet do not appear to add benefit beyond that of mood stabilizers alone. Lithium and lamotrigine have shown benefit for bipolar depression and offer prophylactic benefit. Preliminary evidence for divalproex and topiramate suggest that these and perhaps other mood stabilizers may have similar utility.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), clozapine (Clozaril and others), divalproex (Depakote), gabapentin (Neurontin), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, bupropion, imipramine, lamotrigine, olanzapine, and paroxetine are not approved by the U.S. Food and Drug

Administration for the treatment of bipolar depression; carbamazepine, clozapine, haloperidol, quetiapine, risperidone, topiramate, ziprasidone, and aripiprazole are not approved for the treatment of mania; and clozapine, divalproex, gabapentin, haloperidol, olanzapine, and topiramate are not approved for prophylaxis of bipolar disorder.

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