The Role of Pharmacologic Treatment Guidelines for Bipolar Disorder

Roy H. Perlis, M.D.

With the growth in the number of pharmacologic options available for the treatment of bipolar disorder, clinicians face a challenge in appropriately selecting and sequencing newer and older treatments. Because evidence-based practice has been suggested as a way to improve outcomes across specialties in medicine, a number of practice guidelines and treatment algorithms for bipolar disorder have been developed to aid clinical decision-making. Most of these guidelines and algorithms are based on detailed reviews of the medical literature, with an emphasis on systematic reviews and randomized, controlled trials. Some guidelines incorporate a consensus of expert opinion when the literature does not provide clear evidence. This review examines areas of overlap and discordance in practice guidelines issued by the American Psychiatric Association and the British Association for Psychopharmacology, as well as treatment algorithms developed by the Expert Consensus Guideline Series and the Texas Medical Algorithm Project. *(J Clin Psychiatry 2005;66[suppl 3]:37–47)*

During the past decade, a number of new pharmacologic agents have become available for the treatment of bipolar disorder. In addition to the 7 pharmacotherapies approved by the U.S. Food and Drug Administration for the treatment of some aspect of bipolar disorder, off-label use of other medications is widespread. The opportunities that these new options provide are accompanied by new challenges for clinicians in selecting and sequencing these treatments. One means of assisting clinical decision-making is through the use of treatment algorithms or guidelines. Such tools are based on scientific evidence, a consensus of expert opinion, or both. Within the past 4 years, guidelines have been issued by the American Psychiatric Association (APA),[1] the British Association for Psychopharmacology (BAP),[2] the Expert Consensus Guideline Series,[3] and the Texas Medication Algorithm Project (TMAP).[4] The U.S. Department of Veterans Affairs also has developed a set of guidelines for its hospitals that will not be discussed in this article.[5] The development of these guidelines parallels the emphasis across all specialties on the use of evidence-based medicine, which has the potential to improve the quality, appropriateness, and cost-effectiveness of health care.[6]

Treatment guidelines are generally defined as "systematically developed statements to assist clinician and patient decisions about appropriate health care for specific clinical situations."[2,6] Guidelines such as those published by the APA[1] are based on an extensive review of the medical literature, with an emphasis on systematic reviews and randomized controlled trials. Guidelines also may be derived from both a review of the medical literature and expert opinion, such as those published by the BAP.[2] A common feature of these guidelines is that their principal recommendations and reasonable options are applicable to the average patient. Other guidelines, such as the Expert Consensus Guideline Series,[3] may be based on aggregate opinions drawn from a survey of experts in a particular specialty. Another approach, taken by the Department of Veterans Affairs and the TMAP, is to develop decision trees or algorithms that organize scientific results and expert consensus opinions into recommended treatment sequences. The initial steps in these algorithms are based on controlled studies, and later steps are developed from expert consensus.[7]

The overall goals of all treatment guidelines are to organize scientific evidence and expert consensus into recommended treatment sequences, improve consistency in physician practice by encouraging evidence-based treatment decisions, and discourage the use of ineffective treatments.[6,8]

The complexity of treatment of bipolar disorder probably contributes to the considerable variation in medical practice, including the off-label use of agents for which clear evidence of efficacy in randomized controlled trials

From the Bipolar Clinic and Research Program, Massachusetts General Hospital, Boston.

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Corresponding author and reprints: Roy H. Perlis, M.D., Massachusetts General Hospital Bipolar Clinic and Research Program, 50 Staniford Street, 5th Floor, Boston, MA 02114 (e-mail: RPERLIS@PARTNERS.ORG).

Table 1. Evidence-Based Treatment Guidelines for Acute Mania or Mixed Episode[a]

Level of Intervention	APA	BAP
First-line treatment		
Severe illness	Combination therapy: lithium or divalproex plus antipsychotic[b]	Monotherapy: antipsychotic[b] or divalproex
With agitation	Parenteral antipsychotic if severely agitated	Parenteral antipsychotic and benzodiazepines if severely agitated
Less severe illness	Lithium, divalproex, or atypical antipsychotic[c] Alternatives: carbamazepine or oxcarbazepine in lieu of lithium or divalproex	Lithium or carbamazepine
Short-term adjunctive therapy	Benzodiazepines	Benzodiazepine (eg, clonazepam, lorazepam)
Antidepressants	Should be tapered and discontinued	Should be tapered and discontinued
Differences in management of mixed state	Valproate preferred to lithium	Valproate in irritable dysphoric states only
Breakthrough episode while on therapy		
Manic or mixed episode	Optimize medication dose Introduce or resume atypical antipsychotic	Optimize medication dose Initiate antipsychotic or divalproex
Severely ill or agitated	Short-term adjunctive therapy with antipsychotic or benzodiazepine	Not addressed
Inadequate symptom control with first-line treatment	Add another first-line medication Alternatives: carbamazepine or oxcarbazepine; atypical antipsychotic; switch from one atypical antipsychotic to another (eg, clozapine) Consider ECT	Consider lithium or divalproex plus antipsychotic Consider ECT

[a]Based on American Psychiatric Association[1] and Goodwin.[2]
[b]Atypical antipsychotics are preferred over conventional antipsychotics because of their more benign side effect profile.
[c]Olanzapine or risperidone; alternatives with less supporting evidence for manic or mixed states include ziprasidone and quetiapine.
Abbreviations: APA = American Psychiatric Association, BAP = British Association for Psychopharmacology, ECT = electroconvulsive therapy.

is lacking.[9–12] The evidence of efficacy varies significantly, and comparisons between agents and information on how to sequence them are limited.[13] The absence of such information can lead to the use of medications that have been investigated only in open-label or nonrandomized trials. For example, gabapentin was widely used in the treatment of bipolar disorder after efficacy was suggested in open-label studies. However, gabapentin was not found to be effective in double-blind trials.[9,11]

The use of guidelines may also help in the sequencing of medications. An orderly treatment sequence is necessary for patients with bipolar disorder because frequent or abrupt changes in medication dosage levels can have destabilizing effects.[7] Abrupt decreases in serum lithium levels or complete discontinuation of lithium increases the risk of early relapse into mania or depression[14,15] and raises by 20-fold the risk for suicide within 12 months.[16] A gradual reduction in lithium dosage appears to minimize this risk.[17] Anecdotal evidence also indicates that rapid and frequent changes in mood-stabilizing and antidepressant medications may generally have a destabilizing effect and hasten relapse.[7]

Treatment guidelines may help prevent the use of combinations of medications with the potential for interactions. Valproate and lamotrigine compete for the same glucuronidation enzyme sites in the liver, an action that retards the metabolism of lamotrigine and more than doubles its elimination half-life. If the 2 agents are used in augmentation therapy, lamotrigine treatment should begin at a dose less than half that used in patients not receiving valproate. Similarly, carbamazepine induces the metabolism of other drugs through oxidation and conjugation of cytochrome P450, thus decreasing the availability of valproate, lamotrigine, and many antipsychotics and antidepressants.[1]

TREATMENT GUIDELINE RECOMMENDATIONS

Guidelines for the treatment of bipolar disorder from the APA and the BAP, as well as consensus-based algorithms issued by the Expert Consensus Guideline Series and the TMAP, take subtly different approaches to the management of the 3 major clinical decision points in bipolar disorder: acute mania/mixed episodes, acute depressive episode, and maintenance therapy.[1–4] Of note, both the Expert Consensus Guideline Series and TMAP guidelines are currently being revised, and the revisions were not available for inclusion in this supplement. Areas of overlap and difference in current guidelines are explored in more detail below.

Acute Mania/Mixed Episodes

Evidence-based guidelines. The primary goal of treatment for patients experiencing an acute manic or mixed episode is to control symptoms and allow patients to return to normal psychosocial functioning.[1] The evidence-based guidelines from the APA and BAP recommend the same treatments for both acute manic and mixed episodes and stratify the selection of treatment by severity of illness (Table 1).[1,2]

For severely ill patients, both guidelines recommend that first-line therapy include a mood stabilizer and/or an

Table 2. Consensus-Based Treatment Algorithms for Acute Euphoric/Classic Manic or Mixed/Dysphoric Episodes[a]

Episode	Expert Consensus Guideline Series	TMAP
Acute euphoric/classic manic episode		
First-line treatment	Monotherapy: divalproex,[b] lithium,[b] or carbamazepine[c] alone or with a benzodiazepine	Monotherapy: divalproex or lithium
	Combination therapy: 2 agents (mood stabilizer plus olanzapine,[b] risperidone,[b] quetiapine,[c] or high- or mid-potency conventional antipsychotic)	Combination therapy: 2 agents (eg, lithium, divalproex, oxcarbazepine, antipsychotic)
Next intervention	Divalproex plus lithium[b] or carbamazepine	Divalproex plus lithium
	Lithium[b] or divalproex plus carbamazepine	Carbamazepine plus lithium or divalproex
	If initial regimen included conventional antipsychotic, switch to atypical	
	If initial regimen included atypical antipsychotic, switch to another atypical	
	Alternative: combine conventional and atypical antipsychotic	
Later intervention	ECT; gabapentin, topiramate	Add atypical antipsychotic
		Consider ECT; lamotrigine, gabapentin
Mixed/dysphoric episode		
First-line treatment	Divalproex[b]	Divalproex or carbamazepine
Next intervention	Combination therapy (divalproex plus lithium, divalproex plus carbamazepine, or lithium plus carbamazepine)	Lithium or anticonvulsant
Later intervention	Add lithium or combine divalproex and carbamazepine	Lithium plus anticonvulsant

[a]Based on Sachs et al.[3] and Suppes et al.[4]
[b]Preferred agent.
[c]Alternative agent.
Abbreviations: ECT = electroconvulsive therapy, TMAP = Texas Medical Algorithm Project.

antipsychotic agent, preferably an atypical antipsychotic because of their milder side effect profile with regard to extrapyramidal symptoms.[1,2,18] The 2 guidelines differ in that the APA recommends use of an atypical antipsychotic plus divalproex or lithium, whereas the BAP recommends monotherapy with either an atypical antipsychotic or divalproex but does not specifically mention lithium.[1,2]

Both guidelines recommend combination therapy with a mood stabilizer plus an antipsychotic in some circumstances. Controlled clinical trials of lithium or divalproex plus an antipsychotic suggest that the combinations have greater efficacy or a more rapid onset of action than any of the agents used alone, especially when patients experience breakthrough mania.[1,2] Combinations for which there is good evidence of efficacy include lithium or valproate with haloperidol, olanzapine, risperidone, quetiapine, or ziprasidone.[1,2,19,20]

Severely ill, agitated patients who are unable to take oral medication can receive parenteral administration of an antipsychotic and short-term adjunctive use of a benzodiazepine.[1,2] Ziprasidone and olanzapine are the only atypical antipsychotics currently available in parenteral formulations, and both have been shown effective in randomized, controlled trials.[21,22] Electroconvulsive therapy (ECT) is a consideration for patients who are severely ill, have treatment-resistant mania, express a preference for ECT, or have mixed episodes or severe mania during pregnancy.[1,2]

For patients with less severe illness, the APA recommends monotherapy with lithium, divalproex, or an atypical antipsychotic or short-term adjunctive therapy with a benzodiazepine.[1] There is less supporting evidence for the efficacy of these treatments in manic or mixed states; alternatives included in the APA recommendations are ziprasidone or quetiapine in lieu of another antipsychotic, and carbamazepine or oxcarbazepine instead of lithium or divalproex. The BAP suggests lithium or carbamazepine as short-term therapy for less ill patients.[2]

Consensus-based treatment algorithms. Table 2 summarizes the consensus-based treatment algorithms developed by the Expert Consensus Guideline Series and the TMAP for initial therapy of acute mania.[3,23,24] Unlike evidence-based guidelines that weigh both clinical presentation and severity of illness, consensus-based guidelines consider clinical presentation only and offer sequential approaches to nonresponse. For the first acute manic episode, the Expert Consensus Guideline Series considers 4 clinical presentations: mania with psychosis, dysphoric mania or true mixed mania, euphoric mania, and hypomania.[3] The TMAP algorithm for manic/hypomanic episodes consists of 2 branches, one for euphoric mania and one for mixed mania or rapid cycling.[23]

In contrast to the treatment guidelines that include antipsychotic agents as an option for initial monotherapy, the algorithms focus on initiating therapy for acute euphoric/classic manic episodes with a mood stabilizer (e.g., lithium, divalproex, or carbamazepine). Combinations of a mood stabilizer and either a benzodiazepine or an atypical antipsychotic are alternative first-line treatments in the Expert Consensus Guideline Series.[3,23]

There are slight differences between the treatment algorithms for initial therapy of acute euphoric/classic manic episodes and mixed/dysphoric episodes (Table 2). For first-line therapy of mixed/dysphoric episodes, the Expert Consensus Guideline Series recommendation is monotherapy, preferably with divalproex. Lithium is the first alternative, followed by carbamazepine.[3] Subsequent interventions are the same as those for acute mania. The

TMAP also favors divalproex for initial monotherapy of mixed/dysphoric episodes but includes carbamazepine as another first-line option.[23] TMAP reserves lithium for the next intervention, to be added to initial monotherapy or for use in combination with both divalproex and carbamazepine. Subsequent interventions in the TMAP algorithm are the same as those for pure mania.[23,24]

Breakthrough episodes. When patients experience a breakthrough manic or mixed episode during therapy, both APA and BAP guidelines agree that the first step is to optimize the dose of medication, ensuring that blood levels are within the therapeutic range (Table 1). Initiating or resuming use of an antipsychotic agent is often necessary, particularly if the patient is severely ill or agitated.[1,2] Failure of first-line medications to control symptoms at optimal doses warrants the addition of another first-line therapeutic agent, including an anticonvulsant or an antipsychotic such as clozapine, which is particularly effective in the treatment of refractory illness.[1]

As the next intervention in these patients, the Expert Consensus Guideline Series and the TMAP recommend a combination of mood-stabilizing agents (Table 2). If the initial regimen included an antipsychotic, the Expert Consensus Guideline Series advises switching to another agent within the class or even combining a conventional and an atypical antipsychotic. By contrast, the TMAP does not add atypical antipsychotics until a later stage of treatment.

Later interventions in the Expert Consensus Guideline Series and the TMAP include ECT and gabapentin, which is used as a mood stabilizer despite lack of evidence of its efficacy as adjunctive therapy in bipolar patients with manic, hypomanic, or mixed-state symptoms.[19] The Expert Consensus Guideline Series also includes topiramate, on the basis of preliminary evidence that it may be helpful in mania.[3,25]

Both the APA and the BAP advocate behavioral interventions, although not psychotherapy per se, during manic episodes. Patients may need a calm, highly structured environment that is free of stimuli such as television, videos, music, and even animated conversation. Patients with bipolar disorder commonly exhibit limited insight, especially during manic episodes. They may engage in reckless behavior, and their access to cars, credit cards, bank accounts, and telephones should be limited. Even small changes in mood or behavior may precede the onset of an acute manic episode.[1] Full functional recovery seldom occurs within the first 3 months following remission of mood symptoms. Consequently, patients and their families need advice about withdrawal from work and other responsibilities, if appropriate, and patients should be discouraged from making major life decisions while in a manic or depressive state.[2]

When psychotic features are present, both evidence-based and consensus-based treatment strategies recommend the addition of an atypical antipsychotic to first-line therapy.[1–4]

Acute Depressive Episode

Evidence-based guidelines. Individuals with bipolar disorder generally have longer episodes of depressive than manic or mixed symptoms. A prospective follow-up of 146 bipolar disorder patients who participated in the National Institute of Mental Health's Collaborative Depression Study concluded that, over a mean of 12.8 years, patients spent 3 times as many weeks with depressive symptoms as with manic symptoms (31.9% of follow-up weeks with depressive vs. 9.3% of follow-up weeks with manic symptoms). Depressive symptoms were present 5 times as often as rapid cycling/mixed symptoms (5.9% of follow-up weeks).[26]

Not surprisingly, depression and the severity of depressive symptoms are associated with a greater risk of suicide among bipolar disorder patients. Strakowski and colleagues[27] identified a correlation between higher scores on the Hamilton Rating Scale for Depression (HAM-D) and suicidality in 91 consecutively hospitalized patients with mixed or manic bipolar disorder.

The first-line recommendations of the APA and the BAP for the treatment of acute depressive episodes are shown in Table 3. Both guidelines support the use of a mood stabilizer in combination with an antidepressant as first-line therapy and recommend against the use of antidepressant monotherapy, which may precipitate a switch to mania.[1–3,23]

Most of the recommendations for treating bipolar depression in the APA and BAP guidelines are similar, although they differ in some of their details. APA recommends first-line therapy with either lithium or lamotrigine, noting that more evidence supports the use of lithium than lamotrigine. The BAP guidelines include lamotrigine as first-line therapy for less severe depressive symptoms. However, at least 2 studies suggest that lamotrigine is more effective than placebo in bipolar depression.[28,29]

Both the APA and BAP guidelines support the use of selective serotonin reuptake inhibitors (SSRIs) as the preferred class of antidepressants to be used with lithium or valproate. The APA guidelines note that although monoamine oxidase inhibitors have been shown to have good efficacy, SSRIs have a milder side effect profile. The BAP guidelines state that tricyclic antidepressants are more likely to provoke a switch to mania than SSRIs. Both guidelines recommend the use of an antipsychotic in the presence of psychotic symptoms.[1,2]

The guidelines have similar approaches to severe depression. The APA guidelines advocate simultaneous initiation of lithium and an antidepressant for first-line treatment for patients who are considered to be more severely ill, although data supporting this regimen are limited.[1] APA recommends considering ECT for both severe and

Table 3. Evidence-Based Treatment Guidelines for Acute Depressive Episodes[a]

Level of Intervention	APA	BAP
First-line treatment	Monotherapy: lithium or lamotrigine Antidepressant monotherapy not recommended; consider SSRIs as add-on to lithium or divalproex	Combination therapy: SSRI plus lithium, divalproex, or an antipsychotic for patients with history of mania; antidepressant monotherapy not recommended
More severely ill	Lithium plus antidepressant Consider ECT	Consider ECT
Less severe illness	Not addressed	Consider lamotrigine, lithium, or divalproex initially, despite limited evidence
With psychotic features	Atypical antipsychotic usually required Alternative: ECT	Consider adding atypical antipsychotic
Breakthrough depressive episode during maintenance	Optimize dose of maintenance medication Add lamotrigine, bupropion, or paroxetine Alternative: add different SSRI, venlafaxine, or MAOI	Optimize dose of maintenance medication Address current stressors, if any Ensure current medication (eg, lithium, divalproex, atypical antipsychotic) protects from manic relapse Initiate antidepressant (or consider augmentation/change if currently receiving) Consider SSRI or lamotrigine if prior antidepressant provoked mood instability[b]
Severe	Consider ECT	Add antidepressant to lithium, divalproex, or atypical antipsychotic
Treatment-resistant	Consider ECT	Not addressed

[a]Based on American Psychiatric Association[1] and Goodwin.[2]
[b]Antidepressants are less likely to induce mania when added to lithium, divalproex, or an antipsychotic.
Abbreviations: APA = American Psychiatric Association, BAP = British Association for Psychopharmacology, ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inibitor.

Table 4. Consensus-Based Treatment Algorithms for Bipolar Depression[a]

Level of Intervention	Expert Consensus Guideline Series	TMAP
First-line treatment	Monotherapy: lithium,[b] divalproex, lamotrigine, or carbamazepine[c] alone Combination: lithium,[b] divalproex, lamotrigine,[c] or carbamazepine[c] with antidepressant (eg, bupropion,[b] paroxetine, sertraline, citalopram, fluoxetine, venlafaxine)	Combination: mood stabilizer plus antidepressant (SSRI or bupropion preferred) and lamotrigine
First-line treatment with psychosis	Any mood stabilizer listed above plus antipsychotic (eg, olanzapine,[b] risperidone[b]) and/or antidepressant (any of the above)	Not addressed
Next intervention	Mood stabilizer alone or with antidepressant, add/switch antidepressant or add lithium if taking anticonvulsant	Switch antidepressant; add 2 antidepressants plus mood stabilizer; consider ECT; consider lamotrigine
Next intervention with psychosis	Add antidepressant (eg, bupropion, venlafaxine, or SSRI) to mood stabilizer plus antipsychotic Switch antidepressant or add lithium if on antidepressant, mood stabilizer, and antipsychotic	Not addressed

[a]Based on Sachs et al.[3] and Suppes et al.[4,23]
[b]Preferred agent.
[c]Alternative agent.
Abbreviations: ECT = electroconvulsive therapy, SSRI = selective serotonin reuptake inhibitor, TMAP = Texas Medical Algorithm Project.

treatment-resistant depression.[1] According to the BAP guidelines, severe depression should be treated with an antidepressant in combination with lithium, valproate, or possibly an antipsychotic to reduce the risk of mania.[2] Preliminary results of a large randomized trial showed that olanzapine was significantly better than placebo for bipolar depression, with a therapeutic response evident at the end of the first treatment week.[1,2]

Both guidelines describe ECT as a reasonable alternative for patients with life-threatening inanition, severe depression during pregnancy, suicidality, or psychosis.[1,2]

For less severe symptoms of depression, the BAP recommends initial treatment with lamotrigine, lithium, or valproate.[2]

Consensus-based treatment algorithms. In their approach to bipolar depression, the Expert Consensus Guideline Series and the TMAP overlap in several areas but vary in some of the details (Table 4). Like the treatment guidelines, both algorithms support the use of a mood stabilizer with an antidepressant as first-line therapy and oppose antidepressant monotherapy out of concern for precipitating a switch to mania.[3,23] The TMAP supports initial use of a mood stabilizer (without specifying an agent) and, if a patient responds partially or not at all, adding an antidepressant (bupropion or an SSRI) and lamotrigine, which TMAP classifies as an antidepressant. Subsequent therapy recommendations are to add lithium and switch to a different antidepressant or to add another anti-

Table 5. Long-Term Treatment for Bipolar I Disorder: Evidence-Based Recommendations[a,b]

Level of Intervention	APA	BAP
Initial monotherapy	Lithium or divalproex Alternatives: lamotrigine, carbamazepine, oxcarbazepine ECT if it elicited response in acute episode	Lithium (preferred) Alternatives: divalproex, olanzapine, carbamazepine, oxcarbazepine, lamotrigine ECT if it elicited response in acute episode and patient does poorly on oral agents
Failure to respond to monotherapy	Consider combination therapy; add atypical antipsychotic or antidepressant	If mania predominates: lithium or divalproex plus atypical antipsychotic If depression predominates: lamotrigine, or antidepressant plus lithium or divalproex Consider clozapine
Role of atypical antipsychotic	Reassess need for ongoing antipsychotic if used for acute episode	Helps prevent manic relapse
Adjunctive therapy	Psychosocial intervention	Psychosocial intervention

[a]Based on American Psychiatric Association[1] and Goodwin.[2]
[b]Both the APA and the BAP recommend maintenance medication following a single manic episode.
Abbreviations: APA = American Psychiatric Association, BAP = British Association for Psychopharmacology, ECT = electroconvulsive therapy.

depressant (lamotrigine, venlafaxine, or nefazodone). In case of continued poor response, the TMAP algorithm calls for antidepressant combination treatment, an atypical antipsychotic, or ECT.[4]

The Expert Consensus Guideline Series supports the use of mood stabilizer monotherapy for people with mild-to-moderate depression.[3] The Expert Consensus Guideline Series also advocates initial therapy consisting of monotherapy with a mood stabilizer, with lithium the preferred agent, and divalproex, lamotrigine, or carbamazepine as alternates. An atypical antipsychotic should be added to the mood stabilizer-antidepressant regimen if psychosis is present. Further interventions include adding or switching antidepressants, adding lithium if a patient is receiving an anticonvulsant, and including an antipsychotic if a patient has psychotic symptoms.[3]

Treatment With Antidepressants

The guidelines differ somewhat in their approach to antidepressants after an acute depressive episode, although all advise caution in the use of antidepressants and discourage their use without a mood stabilizer. Antidepressants may be efficacious for acute bipolar depression, but they have not been shown to be more effective than mood stabilizers, especially lithium and lamotrigine, and are less effective in preventing depressive relapse.[30] The results of long-term, double-blind studies showed that tricyclic antidepressants were of limited value in preventing depression in bipolar disorder and were as or less effective than lithium alone.[30]

There is controversy about the appropriate duration of antidepressant therapy for bipolar disorder patients.[2,30] If a patient receiving a mood stabilizer requires antidepressant therapy, the BAP, the Expert Consensus Guideline Series, and others suggest short-term use for 1 to 6 months, after which tapering is desirable.[2,3,31] The APA recommends tapering and discontinuing antidepressants but does not provide a specific time limit.[1] In contrast, a study with 84 patients who achieved remission from bipolar depression concluded that 12 months of antidepressant treatment in combination with a mood stabilizer helps to avoid depressive relapse.[32] However, according to Ghaemi and colleagues,[30] withdrawal depression occurs in about 15% to 20% of patients after recovery from a depressive episode and discontinuation of antidepressants.

In addition to the risk for a switch to acute mania, there is a high risk for long-term mood destabilization in bipolar disorder patients who receive antidepressant monotherapy.[30,31] On the basis of clinical samples, Ghaemi and colleagues[30] estimate that the risk of a short-term manic switch is about 40% with tricyclic antidepressants and about 20% with the newer antidepressants. The risk of long-term mood destabilization/rapid cycling associated with tricyclic antidepressant therapy is about 20%.

Maintenance Therapy

Maintenance therapy is generally recommended after recovery from a single manic or depressive episode to prevent relapse, improve overall functioning, and control subthreshold symptoms, cycling frequency, mood instability, and suicide risk.[1]

First-line maintenance recommendations from the APA and BAP are presented in Table 5, and the Expert Consensus Guideline Series recommendations are in Table 6. The TMAP does not advocate the use of any specific pharmacotherapies for maintenance therapy.[4] All guidelines endorse the continuation of medication(s) to prevent a relapse.[1–4] The APA and the Expert Consensus Guideline Series advocate that the recommended medication(s) used to achieve remission from the most recent depressive or manic episode be continued for long-term maintenance.[1,3] The TMAP algorithm advises continuing the medications that helped achieve remission at the lowest possible effective therapeutic dose.[4]

Most guidelines support the use of lithium either as monotherapy or in a combination regimen in long-term

Table 6. Expert Consensus Recommendations for Long-Term Maintenance After a Manic Episode[a]

Maintenance Phase	Recommendation
Initial maintenance	Continue acute-phase treatment with lithium, divalproex, or both If long-term antipsychotic indicated, add olanzapine,[b] risperidone,[b] or quetiapine[c]
Manic episode during maintenance	If low-dose lithium or divalproex, increase dose and/or add another mood stabilizer (ie, lithium, divalproex, or carbamazepine) If high-dose lithium or divalproex, or lithium plus divalproex at maximum tolerable doses, add another mood stabilizer (carbamazepine[b] or gabapentin[c]) or adjunctive treatment If carbamazepine, increase dose and/or add another mood stabilizer (ie, lithium[b] or divalproex) or continue at same dose and add adjunctive treatments If gabapentin, increase dose and/or add mood stabilizer (lithium,[b] divalproex,[b] or carbamazepine) or adjunctive therapy, or switch to another mood stabilizer If lamotrigine, increase dose and/or add mood stabilizer (lithium,[b] divalproex, or carbamazepine) or adjunctive agent, or switch to another mood stabilizer

[a]Based on Sachs et al.[3]
[b]Preferred agent.
[c]Alternative agent.

treatment.[1–3] The BAP considers lithium the first choice for long-term treatment because it is associated with a reduced risk of suicide and is effective against both manic and depressive relapse, although it is more effective against manic relapse.[2] The APA advises that the best empirical evidence favors use of lithium or divalproex, with lamotrigine, carbamazepine, or oxcarbazepine as reasonable alternatives.[1]

If lithium is poorly tolerated or ineffective, the BAP supports the use of divalproex in preventing manic and depressive relapse; olanzapine for mania; carbamazepine, which BAP terms less effective than lithium, for patients who do not have euphoric mania; and lamotrigine, which prevents depressive more than manic relapse.[2] In continuing the use of the medication a patient was receiving when remission was achieved, the APA guidelines recommend lithium or divalproex or, as alternatives, lamotrigine, carbamazepine, or oxcarbazepine. Only limited information about the efficacy of oxcarbazepine is available, but the agent is included in the APA guidelines because it has efficacy similar to carbamazepine but a milder side effect profile and less potential for drug interaction.[1] The Expert Consensus Guideline Series recommends the use of lithium or divalproex, whichever was more effective in acute treatment, or a combination of the 2 in maintenance therapy.[3]

Among the alternatives to lithium for preventing manic and depressive relapse in patients with treatment-refractory bipolar disorder, divalproex is recommended by the Expert Consensus Guideline Series for use in combination with lithium and, possibly, in triple therapy with lithium and carbamazepine. If a manic episode occurs during maintenance therapy, the Expert Consensus Guideline Series recommends increasing the dosage of the mood stabilizer (lithium, divalproex, carbamazepine, gabapentin, or lamotrigine) or adding another mood stabilizer (lithium plus divalproex or carbamazepine).[3]

Both the APA and BAP guidelines include carbamazepine and, by extrapolation, oxcarbazepine as alternatives, the latter because of its lower potential for drug interactions.[1,2] ECT is an option if it elicited a positive response during an acute episode and if oral medication is ineffective.

The APA and BAP generally do not recommend using antipsychotics in maintenance treatment unless they are required for control of persistent psychosis.[1,2] Because long-term use of antipsychotics, particularly conventional antipsychotics, may cause tardive dyskinesia, the APA recommends that they be slowly tapered and discontinued unless they are needed to control persistent psychosis or provide prophylaxis against recurrence.[1] However, more recent data support the use of atypical antipsychotics. A placebo-controlled relapse-prevention study found continued olanzapine treatment to be superior to lithium monotherapy in patients whose acute episode responded to a combination of lithium and olanzapine.[2] Ziprasidone was shown to provide long-term improvement of symptoms of bipolar mania in a 52-week, open-label study.[33]

For patients who experience a depressive episode while on maintenance therapy, both the APA and the BAP guidelines recommend optimizing the dose of maintenance medication.[1,2] For patients who do not respond to optimal maintenance treatment, the APA recommends the addition of lamotrigine, bupropion, or paroxetine or, alternately, a newer antidepressant (e.g., another SSRI or venlafaxine) or a monoamine oxidase inhibitor.[1] For nonresponsive patients, the BAP recommends initiating antidepressant therapy, increasing the dose, or changing the medication. The BAP also suggests considering lamotrigine if prior antidepressant therapy provoked mood destabilization. BAP guidelines suggest addressing current environmental stressors, if any, and tailoring the treatment regimen to prevent manic relapse.[2]

The Role of Tolerability

The treatment guidelines discussed in this review focus to varying degrees on efficacy data, i.e., whether the efficacy and safety of a drug have been established in

randomized controlled clinical trials. However, it is more difficult for the guidelines to operationalize and weigh tolerability, particularly in the absence of comparative safety data for most newer drugs.

The guidelines recommend the use of certain drugs or classes of drugs because they have fewer adverse events. For example, both the APA and BAP guidelines endorse the use of atypical rather than conventional antipsychotics because of the more benign side effect profile of atypicals,[1] especially in short-term therapy.[2]

In view of the generally high rates of partial or total noncompliance seen in patients with bipolar disorder, tolerability is particularly important in the selection of a therapeutic regimen for long-term maintenance. Some side effects, such as tremor, are a visible marker of illness, while others, such as excessive weight gain, may diminish a patient's feelings of self-worth.[18] A number of studies have shown that extrapyramidal symptoms are associated with poor compliance, and a recent study found a significant positive association between obesity and both subjective distress from weight gain and medication compliance.[34] In addition to initial choice of medication, other strategies to minimize side effects and enhance compliance include dosage adjustments, once-daily administration, and switching medications.[2]

Atypical antipsychotics are expected to play an increasing role in maintenance therapy because they are associated with fewer movement disorders than conventional antipsychotics. However, some of the atypical antipsychotics are associated with significant weight gain and metabolic side effects.[18,35] A meta-analysis[36] of 81 publications that included data on weight gain in patients receiving standard-dose antipsychotic therapy found that weight gain over 10 weeks was greatest with clozapine (4.45 kg), followed by olanzapine (4.15 kg), risperidone (2.10 kg), and ziprasidone (0.04 kg).

The Role of Psychosocial Intervention

Psychosocial intervention, another important component of the overall management of patients with bipolar disorder, receives variable attention from treatment guidelines. The APA guidelines provide a comprehensive review of different psychosocial interventions, and the BAP guidelines include a discussion of cognitive/behavioral therapy. Psychotherapeutic approaches that have undergone formal study include psychoeducational, interpersonal, family, and cognitive/behavioral therapies.[1,2] Compared with treatment as usual, each of these approaches can provide significant benefits for patients and their families. Psychiatrists commonly use a combination of different approaches, depending on a patient's needs and preferences.[1] Use of appropriate psychosocial interventions is especially important in achieving patient adherence to long-term therapy, which is critical to maintaining remission.

CHALLENGES TO DEVELOPING TREATMENT GUIDELINES FOR BIPOLAR DISORDER

The complexity of bipolar disorder renders it an especially challenging disease to control, even for the most experienced clinicians.[4,13] These complexities include psychiatric comorbidities, patients' elevated risk for suicide, and the disorder's chronicity. Given this complexity, developing and applying comprehensive treatment guidelines are especially challenging tasks.[13] Following is an overview of the inherent complexities of bipolar disorder that complicate the development of treatment guidelines and algorithms.

Comorbid or Concurrent Conditions

Concurrent psychiatric illness appears to be the rule rather than the exception in bipolar disorder.[1,13] Data from the National Comorbidity Survey (NCS) showed that all patients with a diagnosis of bipolar I disorder had a lifetime history of at least one other Axis I disorder, 93% had a history of at least one anxiety disorder, and 71% had a history of a substance abuse disorder.[37] Similarly, the Stanley Foundation Bipolar Treatment Outcome Network found that in a study of 288 patients, bipolar disorder was twice as likely to be accompanied by another lifetime Axis I psychiatric disorder (65% of patients), most often an anxiety or substance use disorder, than to exist by itself (35% of patients).[38] Bipolar disorder patients with an anxiety disorder are more likely to have more severe illness than those without a comorbid anxiety disorder.[17] A comparison of the types of anxiety disorders comorbid with bipolar disorder and unipolar major depression[39] concluded that panic disorder and generalized anxiety disorder are significantly ($p < .05$) more common in patients with bipolar disorder than in patients with unipolar depression. The correlation persisted after controlling the results for age, gender, and presence of other anxiety disorders.[39]

Substance abuse, most often with alcohol but also with cocaine or marijuana, also complicates the course of bipolar I disorder. According to NCS data, substance abuse is comorbid in 71.0% of patients with bipolar disorder, alcohol abuse in 64.2%, and drug abuse in 46.1%.[37] In a study of 134 bipolar I subjects,[40] those with past substance abuse had lower rates of remission and a poorer response to lithium than those without a history of substance abuse. Substance abuse also increases the likelihood of poor treatment compliance.[40–42]

Suicidality

Patients with bipolar disorder are at an elevated risk for suicide.[1,13] The frequency of suicide attempts is similar for patients with bipolar I and bipolar II subtypes, and suicide completion rates among patients with bipolar I may be as high as 10% to 15%. Most suicide attempts occur during

depressive episodes or are associated with depressive features during mixed episodes.[1]

Suicide and circulatory diseases are the most common causes of death among patients with bipolar disorder.[43] Standardized mortality rates, which compare observed deaths to expected deaths, were especially elevated for suicide and circulatory disorders in a study of hospitalized affective disorder patients (N = 406) who were prospectively followed for at least 22 years.[43] Patients with bipolar disorder also had a greater risk for death from cardiovascular disorders and all vascular diseases.

Recurrence/Chronicity

Treatment guidelines must account for the fact that bipolar disorder is a lifelong illness, with approximately 40% to 60% of patients failing to achieve a favorable outcome following hospitalization for a manic or mixed episode despite intensive monitoring and treatment.[41,44–46] A larger proportion of patients with bipolar disorder attain syndromal or symptomatic recovery than they do functional recovery after initial hospitalization for mania. In the McLean-Harvard First Episode Mania Study,[46] patients (N = 166) were followed for 2 to 4 years after the initial episode and evaluated for syndromal recovery (no longer meeting criteria for bipolar disorder specified in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition), symptomatic recovery (scores of ≤ 5 on the Young Mania Rating Scale and ≤ 8 on the HAM-D), and functional recovery (resumed premorbid occupational or residential status). By the 2-year follow-up timepoint, 97.6% and 71.7% of the patients achieved syndromal and symptomatic recoveries, respectively. Only 43.1% were functionally recovered at 6 and 24 months; 13.3% achieved and then lost functional recovery within 2 years of hospitalization.[46]

The Stanley Foundation Bipolar Network followed 258 outpatients, 76% of whom had bipolar I disorder, for 1 year following their admission to the network.[44] Despite extensive use of well-accepted therapeutic agents, two thirds of the outpatients experienced intermittent or continuous symptoms that did not respond to treatment. These patients spent a 3-fold greater amount of time depressed than manic.[44] The persistence of depressive symptoms in the first 2 years of follow-up was predictive of depressive symptoms 15 years later, but the early persistence of manic symptoms had no apparent predictive value.[47]

The chronicity of bipolar disorder suggests, first, that clinicians often have to manage patients who have had incomplete medication responses—i.e., they are "better" but not "well." Even patients who have been in remission for several years should continue their medication because they remain at high risk for relapse.[2] Second, in many cases the contribution of any individual medication to improvement may not be clear, particularly for patients who are on combinations of medications. Third, even with the availability of new treatments in the past 5 years, bipolar disorder remains a persistent and severe problem.[44]

Poor Adherence to Medication

Noncompliance with medication regimens is a major contributing factor to a poor clinical course.[13,45] Studies of outpatients with bipolar disorder have reported rates of partial or total noncompliance with treatment ranging from 51% to 64%, regardless of drugs administered.[41,48,49] Noncompliance among patients receiving lithium is widespread.[13] In a 6-year longitudinal cohort study of 1594 subjects treated with lithium,[50] the 75% with a diagnosis of bipolar disorder took lithium for an average of 38% of days, while only 8% followed their prescription for 90% of days during study enrollment.[50]

Subthreshold/Subsyndromal Symptoms

None of the treatment guidelines or algorithms that have been published consider the management of subthreshold or subsyndromal symptoms, which have been defined as manic or depressive symptoms below the levels of hypomania or minor depression symptoms. The combination of subsyndromal, minor depressive, and hypomanic symptoms occurred in 29.9% of weeks, compared with 11.2% of weeks for major depressive and manic syndromes.[26] People who spend more time in subsyndromal than syndromal manic or depressive periods tend to have had better social functioning in the 5 years before their intake episode, shorter duration of the intake episode, a manic-only intake episode, and no history of drug abuse.[26] Medications for manic and depressive syndromal episodes offer only partial protection against subsyndromal symptoms.[46]

Complex Treatment Regimens

A key difficulty in developing treatment guidelines for bipolar disorder is the complexity of the disorder and the complicated treatment regimens that are often used for the disease. Guidelines run the risk of being so complicated that they are unsuitable for use by practicing physicians.[13] Medications from multiple classes, including mood stabilizers, anticonvulsants, antidepressants, and antipsychotics, are commonly applied in the treatment of bipolar disorder. Because monotherapy often cannot control all the symptoms of bipolar disorder or adequately prevent recurrence, combination therapy has become common.[13,51] Lithium and divalproex are often part of augmentation therapy when a patient with acute mania fails to respond to either agent as monotherapy.[51] These 2 agents are also used in combination with certain anticonvulsants, such as carbamazepine, that have mood-stabilizing effects and with the antipsychotic agents haloperidol, olanzapine, risperidone, quetiapine, and ziprasidone for the treatment of acute manic or mixed episodes.[2,20,51] Lithium also is frequently combined with benzodiazepines.[51]

Despite the widespread use of combination therapy, controlled data about its efficacy and safety are available for relatively few combinations.[13,51] Thus, clinicians considering the use of combination therapy have little evidence from randomized, controlled clinical trials to guide dosing and timing of interventions.

CONCLUSION

Contemporary treatment guidelines are more similar than different in their approach to common clinical decision-making in bipolar disorder. For mania, areas in which some discordance exists include the role of atypical antipsychotics and the circumstances in which they should be combined with mood stabilizers. For depression, standard antidepressants receive differing degrees of support. For maintenance, all guidelines advise use of traditional mood stabilizers, but the specific first choice is different across guidelines. Other areas of difference include the relative emphasis on safety and tolerability and the incorporation of psychosocial interventions.

Treatment recommendations agree that a mood stabilizer alone is an appropriate first-line option for acute manic episodes associated with bipolar disorder. Most recommendations include atypical antipsychotics as a therapeutic alternative, although they differ on whether these agents should be used alone or in combination with a mood stabilizer. For acute depressive episodes, all of the recommendations agree that mood stabilizers should be used alone or in combination with an antidepressant. Current recommendations agree that antidepressants should be used only in combination with a mood stabilizer. Additionally, atypical antipsychotics are suggested as part of the therapeutic regimen for patients with psychosis. The various sets of treatment recommendations differ as to whether lithium or divalproex should be the first choice for long-term maintenance therapy, but they agree that the simplest regimen is most appropriate. Psychosocial interventions, often omitted in the past from treatment guidelines, are part of recent evidence-based recommendations that recognize their role in enhancing patient adherence to long-term therapy, which is critical for continued remission.

Future guidelines and algorithms may need to develop recommendations about the role of atypical antipsychotics in long-term maintenance therapy. Current indications are that these agents may have good prophylactic efficacy and, therefore, may be useful in mood stabilization. The distinctions between the long-term roles of mood stabilizers and atypical antipsychotics may blur, possibly leading to the need for future treatment guidelines on this subject.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa), clonazepam (Klonopin and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), nefazodone (Serzone and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, carbamazepine, citalopram, clonazepam, clozapine, fluoxetine, gabapentin, haloperidol, lorazepam, nefazodone, oxcarbazepine, paroxetine, sertraline, topiramate, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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