The Pharmacologic Treatment of Bipolar Disorder

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Over the past half century, substantial clinical trial data have accumulated to guide clinical management of bipolar disorder, and 13 medications have gained US Food and Drug Administration approval for the treatment of mania or bipolar depression or the maintenance treatment of bipolar disorder. While the number of studies has grown and many controversies related to pharmacologic treatment of bipolar disorder are not yet resolved, the task of transforming the accumulated evidence into useful guidance for clinical practice becomes more manageable and less error prone by limiting consideration to the highest quality studies. Therefore, this article emphasizes points of relative clarity by highlighting findings supported by double-blind, placebo-controlled clinical trials with samples of at least 100 subjects. A MEDLINE search was conducted and augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings for randomized controlled trials published in English between 1950 and April 2010 with at least 100 subjects. Keywords used in the search included *randomized controlled trial*, *mania*, *hypomania*, *depression*, *relapse prevention*, *placebo*, *antidepressant*, *switch*, and *maintenance treatment of bipolar disorder*. A paradigm for implementing evidence-based treatment is offered along with consideration of patterns emerging across clinical trials.

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The past half century has seen meaningful growth in the number and quality of studies pertaining to the management of bipolar disorders. The quality of data presented at NCDEU and other academic meetings has advanced from case series and pilot studies to fully powered pivotal trials and recent large-scale effectiveness studies such as those carried out by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) group, the Stanley Foundation, the Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation (BALANCE) group, and the Bipolar Trials Network. The list of evidence-based treatments now includes 13 US Food and Drug Administration (FDA)–approved medications for bipolar disorder.

The yields of drug development efforts directed at meeting the immense needs of patients and families impacted by the common but poorly understood conditions now referred to as *bipolar disorders* are far from satisfying, but do comprise a more scientifically valid basis for clinical decision making than was available through the end of the 20th century. As the admittedly dim light of efficacy and effectiveness data gradually illuminates the clinical landscape, even limited visibility offers opportunities to improve patient care. While acknowledging the continued controversy and uncertainties, this review seeks to emphasize well-established points and areas of general agreement that can provide direction for managing the care of patients with bipolar disorder.

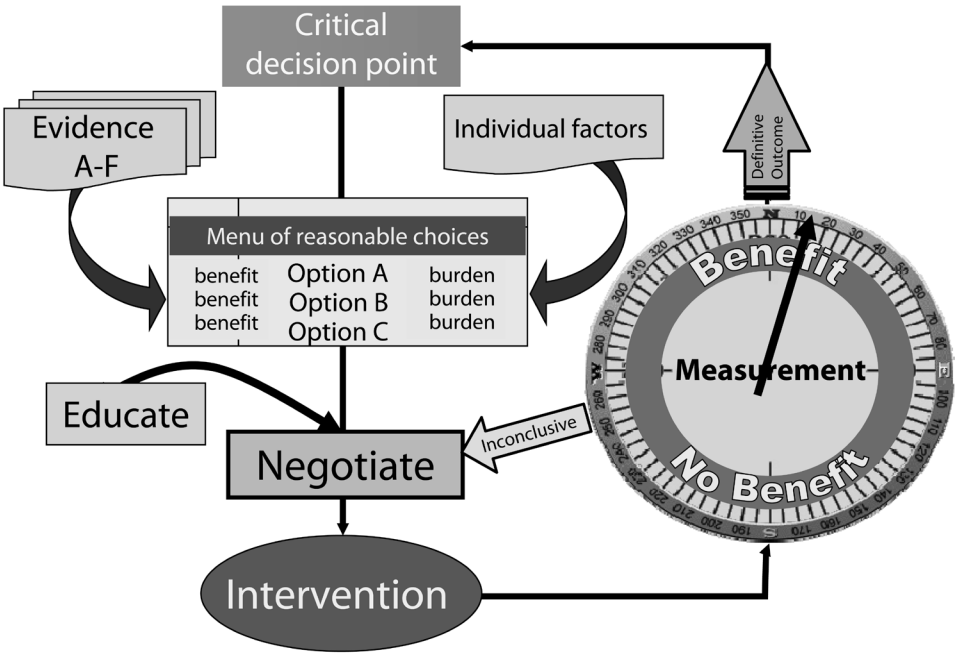
CONTEXT FOR PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

Bipolar disorders are chronic multidimensional conditions afflicting about 3% to 6% of the population.[1–3] Although the illness is often familial, the causes of bipolar disorders remain elusive, and no pathognomonic markers have been identified. Diagnosis is made on the basis of purely clinical criteria. The complexity of symptomatology associated with bipolar disorder often leads to confusion and frustration, which undermine confidence in treatment decisions. A basic fund of knowledge related to bipolar disorder and *DSM-IV* nosology is presented below to facilitate the process of clinical assessment, which is the foundation for management of bipolar illness. After discussion of these issues, an approach is offered to guide the integration of clinical knowledge and evidence from clinical trials.

Typically in bipolar disorder the onset of affective episodes occurs during adolescence or the early adult years.[4,5] Uncertainty frequently plagues the diagnosis, and despite the often dramatic psychopathology observed or reported by patients with bipolar disorders, the rates of false-positive and false-negative diagnosis are high. Field trials suggest that the diagnostic criteria for current acute mania in *DSM-IV* are highly reliable. However, assessment of current hypomania is much less reliable, and it is difficult to determine the reliability of assessments for prior manic or hypomanic episodes, especially when a patient is currently depressed.

The subsequent course of illness is highly variable. Most individuals experience an irregular course in which acute abnormal mood states alternate with periods of full or partial remission lasting weeks to years. While abnormal mood elevation is the cardinal diagnostic feature of bipolar disorders, most patients find depression to be more frequent, and more disabling, than hypomania or mania. Furthermore, abnormal mood states are seldom the only expression of the complex pathophysiology underlying bipolar disorders. In addition to the full syndromal episodes, patients with bipolar disorders often experience functional impairment due to interepisode subsyndromal affective symptomatology,[2,6]

Figure 1. Schema for Iterative Collaborative Measure-Based Care[a]



[a]Adapted with permission from Sachs.[28]

comorbid nonaffective psychopathology[7–16] (eg, anxiety disorders, substance misuse, cognitive impairment), and general medical conditions[17–22] (eg, obesity, migraine headache, inflammatory disorders).

Bipolar disorder ranks as the sixth leading cause of disability worldwide and is associated with increased mortality[23–25] relative to the general population. Suicide accounts for a small fraction of the excess mortality associated with bipolar disorder. Mortality ratios comparing patients with bipolar disorder to the general population reveal elevated death rates due to a number of general medical conditions including heart disease, stroke, and infections.[26,27] The shortened life span of patients with severe mental illnesses like bipolar disorder represents a major health care disparity.

A PARADIGM FOR INTEGRATION OF MEASUREMENT AND MANAGEMENT

The complexity and variability associated with bipolar disorder lead to an understandable desire for a systematic approach to treatment. Stakeholder feedback obtained by the National Institute of Mental Health (NIMH) prior to the start of the STEP-BD made clear that algorithmic care is unattractive to patients and family members as well as clinicians. There is, however, a desire to move clinical practice beyond the guidance of population-based results to personalized care. In response, STEP-BD included a disease management program based on a collaborative chronic care model in which clinicians were encouraged to use their experience and judgment in light of the best available evidence[28] (Figure 1). This model is not the only or necessarily the best model of care. It is presented here because it has been implemented across multiple treatment centers, and, although it is not prescriptive, its use resulted in high rates of treatment concordant with recognized treatment guidelines and in encouraging outcomes.[29]

Table 1. STEP-BD Collaborative Care Model: Principles of Treatment[a]

1. Define critical decision points on the basis of formal diagnostic assessment
2. Formulate a menu of reasonable options for each individual that offers proven treatments first
3. Engage patients in shared decision making and other collaborative care strategies
4. Integrate measurement into management
5. Revise the menu of reasonable choices on the bases of response and tolerability

[a]Based on Sachs.[30]
Abbreviation: STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

The STEP-BD Collaborative Care model involves 5 main principles[30] (Table 1). The model starts with the assumption that the patient meets formal diagnostic criteria for bipolar disorder, agrees to at least 1 treatment objective, and confronts a critical clinical decision point. These decision points are most commonly related to management of acute episodes (depression, hypomania, mania, or mixed), but may be relapse prevention, return to employment, control of rapid cycling, desire to conceive a child, or management of a treatment-limiting adverse effect.

Table 2. Simplified Levels of Evidence[a]

Category A	Double-blind placebo-controlled trial with adequate sample[b]
Category B	Double-blind comparison studies with adequate sample[b]
Category C	Open comparison trials with adequate sample[b]
Category D	Uncontrolled observation or controlled study with ambiguous result
Category E	No published evidence (± class effect)
Category F	Available evidence negative or considered a failed trial

[a]Based on Sachs.[28]
[b]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.

In this model, clinicians formulate a personalized menu of reasonable choices based on consideration of both the best available evidence pertaining to the current decision point and the clinician's knowledge of the patient as an individual. Evidence-based practice recognizes an implicit duty to at least offer proven treatments first.[31] Clinicians can meet this duty by maintaining a working knowledge of the proven treatments defined in Table 2 as "category A" treatments and by being aware of the key individual characteristics of their patients that pertain to choice of treatment. At a minimum this will include a patient's history of prior treatment response, adverse effect tolerance, pertinent general medical conditions, and personal preferences. Essential to collaborative care is the concept of having a plan with shared decision making and communication with other professionals and those the patient designates as supports. Including the patient as an active agent in his or her own care requires an engaged, well-informed patient and negotiation skills. Given the opportunity, patients and their care providers are often motivated to make a well-informed selection from the menu of reasonable choices and participate in a variety of self-management strategies. The outcome of each intervention is then evaluated on the basis of routine measures. The measures for assessing the benefit of an intervention may consist of formal scales or judgments made in reference to a patient's personal goals.

When interventions are carried out to a definitive endpoint (declaring that a treatment is effective, ineffective, or intolerable), it is possible to make progress toward optimizing an individual's treatment plan. Indecisive outcomes, however, may result when tolerable interventions are curtailed without adequate dose or duration or are simply rejected as unacceptable. Integrating measurement into the management facilitates personalized evidence-based treatment decisions.

Several lines of evidence support the rationale of retaining well-tolerated, efficacious treatments and replacing treatments that are ineffective and/or poorly tolerated.[32–34] Keeping records of these outcomes facilitates optimization of an individual's treatment plan through iterative revision of the menu of reasonable choices. No currently available biomarker or group of biomarkers offers a better means of guiding treatment decisions.

Importantly, several studies indicate that a patient's record of response to treatment has impressive predictive value. For subjects (N = 3,369) enrolled in 10 placebo-controlled pivotal trials for bipolar depression, Calabrese et al[35] examined the value of "early response" (defined as improvement in the depression scale score of at least 20% from baseline after 2 weeks of treatment) for predicting the probability of response and remission at the end of each study (7–10 weeks of treatment).

The most compelling finding in this analysis was the high negative predictive value associated with not meeting the criteria for early improvement. Across all of the 10 active treatment groups as well as the placebo groups, subjects with less than 20% improvement after 2 weeks of treatment had only a 10%–20% chance of meeting remission criteria at the end of the study.[35] The consistency of this pattern observed across large placebo-controlled studies for bipolar depression suggests that a determination of the need for dose adjustment or a declaration of the treatment as ineffective could be made with acceptable confidence as rapidly as every 2 weeks.

EVIDENCE: DECISION MAKING GUIDANCE AND BENCHMARK METRICS

Implicit in the general consensus that the principles of evidence-based medicine provide the best guidance for clinical practice is the idea of offering proven treatments before unproven treatments.[31] Utilizing this principle necessitates a working knowledge of medical evidence and consideration of appropriate metrics. Consumers of medical evidence can assess the clinical meaning of published studies by evaluating the quality of the evidence, by gauging the effect size of various interventions, and by establishing benchmarks applicable to routine clinical practice. Simple metrics are offered below to integrate these processes into meaningful guidance for clinical decision making and metrics for evaluating outcomes in routine practice.

For the purposes of this review, we conducted a MEDLINE search augmented by a manual search of bibliographies, textbooks, and abstracts from recent scientific meetings to identify randomized studies of mania, hypomania, depression, or maintenance treatment of bipolar disorder with at least 100 subjects. Although areas remain for which few or no high-quality data are available, the knowledge base pertaining to clinical care of patients with bipolar disorder has grown substantially over the past 2 decades. The daunting task of transforming the accumulated evidence into useful guidance becomes more manageable and less error prone by limiting consideration to the highest quality studies. Results from studies with sufficient methodological rigor to allow valid causal inference, referred to here as *category A evidence*, represent the highest standard for evidence-based medicine (Table 2). Category A evidence is derived from randomized double-blind placebo-controlled studies with sample sizes adequate to detect differences that are statistically significant and clinically relevant. Formal power calculations to determine sample size adequacy can be complicated. A simple

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rule of thumb, however, is often sufficient to help clinicians judge the adequacy of sample size in mood disorder treatment studies. Clinical trials with fewer than 100 subjects are unlikely to meet criteria for category A evidence.

This simple benchmark establishes a lower bound on the range of studies we include as having high-quality evidence.

EVIDENCE REVIEW: MANIA

Cade's 1949 publication[36] on the calming effects of lithium was a landmark event setting the stage for an era of progress in psychopharmacology. This case series was followed by persuasive, albeit small, placebo-controlled crossover studies. The first parallel-group placebo-controlled trial for demonstrating the acute antimanic efficacy of lithium did not appear in the literature until 1994.[37]

As seen in Table 3, category A studies for acute mania now demonstrate the efficacy of 8 dopamine-blocking agents (olanzapine,[46,47] ziprasidone,[53,54] risperidone,[49–52] haloperidol,[49] quetiapine,[55–60] aripiprazole,[61–63] paliperidone,[66] and asenapine[64,65]) and 3 non–dopamine-blocking agents (lithium,[37–39] valproate,[37,40] and carbamazepine[42,43]).

Due to the less stringent standards of the mid–20th century, chlorpromazine has FDA approval for mania but lacks a placebo-controlled trial establishing its antimanic efficacy. In a comparison of lithium to chlorpromazine (n = 255), Prien et al[38] found both to be effective for mania, but chlorpromazine (mean dose = 1,000 mg) was more effective in severely ill and agitated patients, while lithium (mean dose = 1,800 mg) was associated with fewer adverse effects.

The available data indicate that 3 weeks of monotherapy treatment with any of these FDA-approved agents is significantly more beneficial than placebo treatment, but seldom sufficient to achieve a complete remission of manic symptoms. After 3 weeks of treatment under the controlled conditions of a randomized controlled trial (RCT), the mean mania rating scale score for subjects receiving any one of the proven antimanic agents still exceeds the minimum symptom score required for study entry at baseline.* This finding highlights the need for sustained treatment and provides a rationale for combination treatment.

While there are undoubtedly individual differences in response to antimanic agents, the preponderance of accumulated evidence does not indicate important differences in overall efficacy. Nearly all direct comparisons between active agents yield no statistically significant differences in overall antimanic efficacy (lithium vs chlorpromazine,[38] haloperidol vs risperidone,[49] olanzapine vs divalproex,[68] olanzapine vs haloperidol,[69] aripiprazole vs haloperidol,[70] quetiapine vs lithium,[39] quetiapine vs hapoleridol[67]). Two exceptions to this pattern are noteworthy. Tohen et al[71] found olanzapine to have a small, but statistically significant efficacy advantage over divalproex. This advantage was, however, at least partially offset by disadvantages in tolerability. Conversely, the comparison of aripiprazole and haloperidol reported by Vieta et al[70] found no difference in efficacy, but a significant advantage for aripiprazole in overall effectiveness due to its greater tolerability.

Number needed to treat (NNT) analyses of the positive category A studies show that for a mania RCT to yield 1 additional responsive subject above the placebo response rate, it is necessary to treat 3 to 6 subjects with a proven antimanic agent. The desire to compare results across studies by comparing effect size is understandable, but making comparisons of the NNT across studies is of questionable validity. An NNT analysis does correct results for placebo response, but does not overcome the methodological limitations that prevent drawing conclusions based on comparisons of treatment other than those available within a single randomized study. Comparing outcomes across placebo-controlled monotherapy mania studies is confounded by differences in study samples as well as study procedures. For instance, the antimanic efficacy of risperidone appears twice as robust in study results based on a sample accessioned in India[52] compared to results obtained in a separate study that used nearly the same treatment protocol but enrolled its sample exclusively at sites in the United States.[51]

Category A studies suggest that adding a dopamine-blocking antimanic agent confers about the same increment of extra benefit over placebo whether used as monotherapy or administered as an adjunct to valproate or lithium.[72,73] Valproate was also superior to placebo as an adjunct to antipsychotic treatment.[74]

The available data are as yet insufficient to conclusively prove that 2 agents are superior to monotherapy, because the advantage of adding a second active agent has been demonstrated only in samples that restricted enrollment to subjects with inadequate response to prior treatment. Nonetheless, combination treatment is a reasonable approach for more severely ill patients, since the preponderance of evidence

Table 3. Summary of Category A Acute Mania Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lithium[37–39]	Lamotrigine[c]	✓
Valproate[37,40]	Gabapentin[41]	
Carbamazepine[42,43]	Oxcarbazepine[44]	
	Topiramate[45]	✓
Olanzapine[46,47]	Licarbazepine[48]	
Risperidone[49–52]		
Ziprasidone[53,54]		
Haloperidol[49]		
Quetiapine[55–60]		
Aripiprazole[61–63]		
Asenapine[64,65]		
Paliperidone[66]		

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.
[c]G.S.S., GlaxoSmithKline data on file, 2000.

*References 37, 39, 46, 47, 51–54, 57, 58, 61–67.

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from these studies shows lower dropout rates among subjects receiving 2 active treatments than those receiving placebo and 1 active treatment.[75,76]

In addition, placebo-controlled adjunct studies have established the efficacy of adding valproate to dopamine-blocking agents[74] and the efficacy of adding risperidone, haloperidol, olanzapine,[49] or quetiapine[55] to the non–dopamine-blocking agents lithium and valproate.

Category A placebo-controlled clinical trials comparing gabapentin, lamotrigine, topiramate, oxcarbazepine, and licarbazepine to placebo have to date produced only negative results or failed studies (references 41, 44, 45, 48, and 77 and G.S.S., GlaxoSmithKline data on file, 2000). These results do not support a class effect for anticonvulsants as antimanic agents.

Table 4. Summary of Category A Acute Bipolar Depression Efficacy Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lamotrigine[83]	Imipramine[84]	
Olanzapine[80]	Paroxetine[85]	✓
Olanzapine and fluoxetine[80]	Lithium[86]	✓
Quetiapine[85–89]	Aripiprazole[90]	
	Ziprasidone[91]	
	Bifeprunox[92]	
	Lithium + paroxetine[78]	
	Lithium + imipramine[78]	
	Mood stabilizer + paroxetine[93]	
	Mood stabilizer + bupropion[93]	

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.

EVIDENCE REVIEW: DEPRESSION

A variety of scientific, ethical, and practical design issues have long hampered efforts to address basic clinical questions related to bipolar depression, and consequently most studies examined adjunctive treatment.[78–80] Early studies suggesting benefit of monoamine oxidase inhibitors (MAOIs) are limited by small sample size and classification of outcomes based solely on change in depression scale scores.[81,82] Thus, reported response rates were not corrected for subjects who experienced treatment-emergent switch to hypomania or mania. Recent parallel-group double-blind studies of bipolar depression have improved methodology, and results for monotherapy including lithium, atypical antipsychotics, and standard antidepressants are becoming available.

The evidence review process identified 11 medication (monotherapy or combination) treatments for which category A studies have been conducted (Table 4). Positive category A evidence clearly supports the 2 FDA-approved treatments, quetiapine[85–89] and the combination of olanzapine and fluoxetine (OFC).[80] The same 3-arm study that established the efficacy of OFC also found olanzapine monotherapy had significantly better efficacy than placebo for bipolar depression. In that study, the combination of olanzapine and fluoxetine was statistically superior to olanzapine monotherapy as well as superior to placebo.[80] Two positive category A studies support the use of lamotrigine for acute bipolar depression.[83,94] Lamotrigine does not, however, have FDA approval and has had 4 additional negative or failed studies.[95]

To date, only 1 category A study is available with data comparing lithium to placebo as a treatment for acute bipolar depression. This study must be considered a negative study rather than a failed trial for lithium, because the study found no difference between lithium and placebo, while also finding statistically significant advantage for quetiapine over placebo.[86]

Whenever multiple proven treatments exist, the question arises of which treatment might be best for an individual patient. While matching treatments to individual patients remains an unfulfilled dream, in this instance there may be some clinically interesting pharmacogenetic light at the end of the proverbial tunnel. Perlis et al[96] found a differential pattern of response based on genotypes of subjects randomly assigned to treatment with OFC (n = 88) or lamotrigine (n = 85). A set of 19 candidate genes were genotyped. Response to OFC was significantly associated with single nucleotide polymorphisms (SNPs) within the dopamine D_3 receptor and histamine H_1 receptor (*HRH1*) genes. Response to lamotrigine was significantly associated with SNPs within the dopamine D_2 receptor, *HRH1*, dopamine β-hydroxylase, glucocorticoid receptor, and melanocortin 2 receptor genes. These findings are consistent with the notion that dopaminergic influences play an important role in bipolar I depression.

Several dopamine-blocking antimanic agents (bifeprunox,[92] aripiprazole,[90] and ziprasidone[91]) have produced negative or failed results in bipolar depression studies. This may reflect real differences in the action of these drugs in comparison to quetiapine and olanzapine, but may also result from simple deficiencies in the design and execution of the clinical trials. In addition to disadvantages related to inadequate knowledge of the therapeutic doses of these medications for bipolar depression, some of the trials were quite likely hampered by enrollment of inappropriate subjects and/or low quality ratings on study outcome measures.[97,98]

The role of standard antidepressants in bipolar depression remains controversial. Baldessarini et al[99] reported that despite the ongoing concern about prescribing unopposed antidepressant medication to bipolar patients, antidepressant medication is still the initial treatment for 50% of newly diagnosed patients with bipolar disorder in the United States. Unfortunately, there are few data to support the benefit of this common practice.

A meta-analysis of small double-blind studies is often cited as evidence supporting the adjunctive use of standard antidepressants as a class for the treatment of bipolar depression.[100] The utility of this meta-analysis as a guide to treatment is unclear for several reasons. First,

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the class of drugs referred to as *antidepressants* is heterogeneous in structure and mechanism (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, MAOI, etc). Second, data from studies of MAOI-type antidepressants constitute a large proportion of the positive data and, as noted above, tend to overestimate the benefit of treatment because subjects were considered antidepressant responders even if they switched to mania during the course of treatment. Third, no individual standard antidepressant has shown efficacy in a category A study as monotherapy nor as an adjunct to lithium or valproate. Furthermore, the results of recent efficacy and clinical effectiveness studies have not produced results that encourage use of standard antidepressants for bipolar depression.

In a double-blind study comparing placebo to standard antidepressants (bupropion or paroxetine) as adjuncts to mood stabilizers for bipolar depression, STEP-BD found no advantage for standard antidepressants over placebo.[93] Separately, STEP-BD used the same infrastructure and outcome measures to conduct a quasi-experimental analysis comparing outcome for STEP-BD subjects who did not participate in the randomized trial, but were prescribed antidepressant medications while participating in the study. This open comparison of the outcome for depressed bipolar patients treated with or without standard antidepressant medications also showed no advantage for adjunctive antidepressant medication.[101,102] It is important to note, since study results are often viewed as subject to the limitation of accession bias, that results from the sample receiving open treatment were remarkably similar to results obtained from subjects who consented to participate in the double-blind study. In both studies, the proportion of patients who achieved a durable recovery (defined as 8 consecutive weeks of euthymia) was less than 25%.

Another large effectiveness study conducted by the Stanley Foundation Bipolar Network reported similar discouraging results for standard antidepressants. Altshuler et al[103] found that only about 15% of bipolar depressed patients for whom an antidepressant was prescribed in open treatment met criteria for treatment response.

Very limited data are available to guide the treatment of depression in patients with bipolar II disorder. Suppes et al[104] reported that the benefit of quetiapine was significantly superior to placebo in the subset of more than 180 bipolar II subjects randomized in 2 bipolar depression studies. In a study with a smaller bipolar II sample, however, Suppes et al[88] found that the antidepressant benefit of quetiapine extended release reached statistical significance in bipolar I but not bipolar II subjects.

Amsterdam[33,105–108] has published several papers with small samples suggesting that patients with bipolar II might safely be treated with standard antidepressants. The small studies require follow-up in fully powered controlled trials, but do offer some support for the idea that there may be subsets of bipolar II patients who benefit from standard antidepressant medication, even as monotherapy.

TREATMENT-EMERGENT AFFECT SWITCH

Prior to the advent of modern antimanic and antidepressant medications, Emil Kraepelin recognized that patients with manic-depressive illness frequently make direct transitions from one affective state to another of opposite polarity, without an intervening period of recovery.[109] The possibility that pharmacologic agents capable of treating mania or depression might lead to treatment-induced mania or depression has long been a serious concern for the field.[110–116]

Unfortunately, we lack methods to confidently determine whether any given transition between pathological mood states is iatrogenic or due to the natural course of an individual's illness. Therefore, referring to *treatment-emergent depression, hypomania, mania,* or *mixed episodes* is more accurate than using terms such as *antidepressant-induced mania* or *neuroleptic-induced depression*.

Despite several trials that have reported rates of treatment-emergent affect switch (TEAS), the extent to which standard antidepressant medications are associated with treatment-emergent hypomania or mania remains highly controversial. Rather than rehashing this unsatisfying debate, a summary of the data can provide some practical guidance for clinical practice.

None of the medications with category A evidence of efficacy for bipolar depression has been associated with treatment-emergent hypomania/mania. STEP-BD found no evidence of TEAS associated with adjunctive use of bupropion or paroxetine compared to adjunctive placebo.[93] The Stanley Foundation Bipolar Network found that venlafaxine was associated with significantly higher rates of TEAS than bupropion or sertraline.[117] Furthermore, the same study found that among subjects randomly assigned to these 3 antidepressants, overall TEAS rates were significantly higher among bipolar I subjects compared to bipolar II subjects.[118] Defining TEAS as a Young Mania Rating Scale score > 13, they observed a TEAS rate of 12% (of 134) of bipolar I subjects versus 2% (of 48) of bipolar II subjects. Defining TEAS as a Clinical Global Impressions (CGI) mania score of ≥ 3 (mildly ill) produced observed rates of 22% in bipolar I subjects and 8% of bipolar II subjects.

These findings suggest that there may be important differences between agents classified as "antidepressants" in regard to the propensity to induce affective switch. On the other hand, the putative destabilizing effect of standard antidepressants may be a reflection of a relatively small vulnerable subgroup. When standard antidepressants are administered as adjuncts to an antimanic mood stabilizing agent, 80% to 90% of subjects do not experience TEAS.

A recent review by Frye et al[119] identified risk factors associated with TEAS: tricyclic antidepressant use, prior history of treatment-emergent mania, hyperthymic temperament, comorbid alcoholism, female gender, comorbid anxiety disorder, prepubertal onset, and bipolar I subtype (vs bipolar II). The effect sizes of most, if not all, of these factors are likely to be modest and have little predictive

power for individual care. Perhaps the least controversial recommendation that can be applied in clinical practice is to avoid repeating exposure to any class of medication that has been associated with a personal history of TEAS.

EVIDENCE REVIEW: MAINTENANCE, OR PREVENTION OF RECURRENCE

Although lithium was granted FDA approval as a prophylactic treatment for bipolar disorder in 1974, the first adequately powered parallel-group double-blind placebo-controlled RCT was not published until 2000.[120] This industry-sponsored study was designed as a pivotal trial to evaluate the prophylactic utility of divalproex versus placebo and included a lithium arm to establish assay sensitivity. Although widely considered a failed trial because differences on the a priori primary outcome measure did not reach statistical significance and no benefit of lithium was detected, the study did produce several important findings. Divalproex was not significantly better than placebo on the a priori primary outcome variable, time to any mood episode. Divalproex was, however, superior to placebo on some important secondary outcome variables including lower rates of discontinuation for a recurrent mood episode and discontinuation due to a depressive episode. Divalproex was also superior to lithium for protection against depressive symptoms and on Global Assessment Scale scores. More importantly, post hoc analyses suggested that the study failed because a substantial number of subjects were randomized who were not ill at the time of enrollment and therefore not necessarily responders to acute treatment with divalproex.

In light of this problem, subsequent successful maintenance treatment studies have employed designs in which the randomized sample is enriched with responders to open acute treatment with the study drug. Furthermore, in studies with enriched design, subjects randomly assigned to placebo are actually discontinuing treatment with the study drug that had been associated with sufficient improvement to qualify them for the double-blind phase of treatment. Meta-analyses of maintenance studies show that previously stable patients suffer high relapse rates following discontinuation of medication, especially when discontinuation is rapid.[121–130] These studies, which typically show survival curves with steep slopes for the placebo group in the first months after randomization, can more accurately be considered treatment-disruption studies. Recognition of this design issue has important ramifications for understanding clinical trial results.

In an NIMH-sponsored study designed to compare the benefit of prophylactic treatment with lithium at low (0.4–0.6 mmol/L) versus standard levels (0.8–1.0 mmol/L), Gelenberg et al[131] found a significant advantage for treatment at standard levels. The risk of relapse was 2.6 times higher in those randomly assigned to the lower range treatment. A reanalysis of these data suggested that the higher relapse rate associated with lithium treatment at the low level was really driven by the high relapse rate experienced by subjects who had an abrupt 50% reduction in their dose of lithium as a consequence of randomization to switch from the standard range to the low range. Furthermore, subjects who stayed at the standard range had no advantage over subjects who started and remained at the low range. Thus, an abrupt reduction of even 50% may adversely impact the course of illness in stable patients.

Table 5. Summary of Category A Prophylaxis Studies[a]

At Least 1 Positive Trial	Only Negative or Failed Trials	Negative Study[b]
Lithium[94,133,134]	Imipramine[84]	✓
Valproate[94,120,133,134]		
Lamotrigine[94,133,134]		
Olanzapine[34,135,136]		
Aripiprazole[137]		
Quetiapine[138]		
Ziprasidone[139]		
Risperidone[140]		

[a]Statistical power ≥ 0.8 to detect meaningful differences at $P < .05$.
[b]Interpreted as a "negative study" because the study drug failed to separate from placebo and the study included an active comparator that did separate from placebo.

Although most of the relapse prevention data come from studies of agents with acute antimanic activity, similar results are reported following treatment of acute bipolar depression.[94] In a small double-blind study, Ghaemi et al[132] found trends that reached borderline statistical significance indicating worsening course following discontinuation of effective antidepressant medications.

In a 3-arm prophylaxis study that randomized 117 bipolar I subjects but did not include placebo, Prien et al[84] reported that lithium and lithium plus imipramine were superior to imipramine alone in preventing recurrences of mania and found no significant differences between the 3 conditions for prevention of depression.

As seen in Table 5, category A studies support the use of lithium,[94,133,134] lamotrigine,[94,133,134] olanzapine,[34,135,136] aripiprazole,[137] quetiapine,[138] ziprasidone,[139] and the long-acting injectable form of risperidone[140] for preventing recurrence of acute episodes. These successful category A studies, however, all randomized patients who had experienced a remission of acute phase symptoms during treatment with the study medication prior to randomization. This methodological issue has important clinical implications. The data from these successful maintenance studies cannot support the practice of switching from acute phase treatments to a new maintenance treatment after resolution of an acute episode. Instead, the data provide persuasive argument against treatment disruption and support continued treatment with agents that were a part of a successful acute phase regimen.

The BALANCE study[141] was a large simple trial designed to compare long-term outcomes of treatment with lithium, valproate, and the combination of lithium and valproate in subjects who were not acutely ill, but warranted maintenance treatment. Consenting bipolar subjects all started 4 to 8 weeks of open treatment with the combination of lithium and

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valproate. Subjects (n = 330) were then randomly assigned to continuing combination treatment, lithium monotherapy (by tapering off valproate) (plasma concentration, 0.4–1.0 mmol/L), or valproate monotherapy (by tapering off lithium) (750–1250 mg). The primary outcome was time to intervention (either medication or hospitalization), and patients could be randomized without necessarily being euthymic. Although the hazard ratio for combination therapy versus lithium monotherapy was 0.82 (95% CI = 0.58–1.17, $P = .27$), the difference was not statistically significant. The study did, however, find a significant advantage for combination treatment compared to valproate monotherapy (hazard ratio = 0.59, 95% CI = 0.42–0.83, $P = .0023$). This finding may not be generalizable due to the low valproate dosage used, but it at least informs practitioners that low-dose valproate maintenance treatment is of little merit.

Like other studies above, BALANCE used a discontinuation paradigm. Notably, the study was enriched only to the extent that randomized subjects were able to tolerate the combination of lithium and valproate rather than necessarily respond to combination treatment. The apparent disagreement between this study and the Bowden et al report[37] may simply reflect the difference in entry criteria, dosing, and definition of outcome, but it is also possible that maintaining therapeutic lithium levels protects against recurrence due to valproate discontinuation, while valproate as dosed in BALANCE does not protect against recurrence due to lithium discontinuation.

Individual factors reported as associated with relapse and poor outcome for bipolar disorders include early age at onset, psychosis,[142] psychiatric comorbidities,[143–145] residual mood symptoms,[146,147] history of frequent episodes,[143,148,149] and use of antidepressants.[111] In women with bipolar disorders, postpartum[150] and the menopause transition[151] are also periods of increased vulnerability to illness relapse. Consistent with early reports suggesting familial response to lithium,[152] Perlis and colleagues[153] have reported several genes with modest association to lithium response in both the STEP-BD and University College London cohorts. Large-scale genome-wide association studies have promise to identify predictors of individual response to specific prophylactic treatments.

CONCLUSIONS

Bipolar disorders are common chronic complex conditions. Accumulated clinical trial data now offer a scientific basis for clinical decision making. No clinically useful biomarkers have been identified for predicting treatment response. A systematic iterative approach to treatment in which measurement is integrated into the management plan offers a means to bridge from population-based recommendations to personalized care. The distinction between efficacy and effectiveness research includes at least tacit recognition of potential individual differences in response to treatment and the importance of care delivery systems.

Patients with acute mania vary widely in symptomatology and clinical urgency. Although dopamine-blocking agents appear to be preferable for more severely ill patients, non–dopamine-blocking antimanic agents may be more tolerable. Most often, treatment over a period of 3 to 4 weeks is insufficient to achieve full remission. The data support a class effect for dopamine-blocking agents but not anticonvulsants as treatment for acute mania.

Four treatments have positive category A evidence for the treatment of bipolar depression. There is no evidence that adding standard antidepressant medication destabilizes patients treated with agents that have proven antimanic efficacy.

All agents with proven efficacy for relapse prevention have gained approval based on studies that randomized patients who had already improved in response to study medication. This so-called enriched design is an important limitation on the generalizability of results from relapse prevention studies, but has consistently replicated the finding that abrupt discontinuation of treatment can destabilize bipolar patients.

More research and further refinement in methodology are needed to facilitate the translation of population-based data to personalized treatment.

Drug names: aripiprazole (Abilify), asenapine (Saphris), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), topiramate (Topamax and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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