REVIEW ARTICLE

Diagnosis and Treatment of Bipolar Disorders in Adults: A Review of the Evidence on Pharmacologic Treatments

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BACKGROUND: Patients with bipolar disorder are exceptionally challenging to manage because of the dynamic, chronic, and fluctuating nature of their disease. Typically, the symptoms of bipolar disorder first appear in adolescence or early adulthood, and are repeated over the patient's lifetime, expressed as unpredictable recurrences of hypomanic/manic or depressive episodes. The lifetime prevalence of bipolar disorder in adults is reported to be approximately 4%, and its management was estimated to cost the US healthcare system in 2009 $150 billion in combined direct and indirect costs.

OBJECTIVES: To review the published literature and describe the personal and societal burdens associated with bipolar disorder, the impact of delays in accurate diagnosis, and the evidence for the clinical effectiveness of available pharmacologic therapies.

METHODS: The studies in this comprehensive review were selected for inclusion based on clinical relevance, importance, and robustness of data related to diagnosis and treatment of bipolar disorder. The search terms that were initially used on MEDLINE/PubMed and Google Scholar were restricted to 1994 through 2014 and included "bipolar disorder," "mania," "bipolar depression," "mood stabilizer," "atypical antipsychotics," and "antidepressants." High-quality, recent reviews of major relevant topics were included to supplement the primary studies.

DISCUSSION: Substantial challenges facing patients with bipolar disorder, in addition to their severe mood symptoms, include frequent incidence of psychiatric (eg, anxiety disorders, alcohol or drug dependence) and general medical comorbidities (eg, diabetes, cardiovascular disease, obesity, migraine, and hepatitis C virus infection). It has been reported that more than 75% of patients take their medication less than 75% of the time, and the rate of suicide (0.4%) among patients with bipolar disorder is more than 20 times greater than in the general US population. Mood stabilizers are the cornerstone of treatment of bipolar disorder, but atypical antipsychotics are broadly as effective; however, differences in efficacy exist between individual agents in the treatment of the various phases of bipolar disorder, including treatment of acute mania or acute depression symptoms, and in the prevention of relapse.

CONCLUSION: The challenges involved in managing bipolar disorder over a patient's lifetime are the result of the dynamic, chronic, and fluctuating nature of this disease. Diligent selection of a treatment that takes into account its efficacy in the various phases of the disorder, along with the safety profile identified in clinical trials and in the real world can help ameliorate the impact of this devastating condition.

Bipolar disorder is a chronic, relapsing illness characterized by recurrent episodes of manic or depressive symptoms, with intervening periods that are relatively (but not fully) symptom-free. Onset occurs usually in adolescence or in early adulthood, although onset later in life is also possible.[1] Bipolar disorder has a lifelong impact on patients' overall health status, quality of life, and functioning.[2]

This disorder has 2 major types—bipolar disorder I and bipolar disorder II.[3] Bipolar disorder I is defined by epi-sodes of depression and the presence of mania, whereas bipolar disorder II is characterized by episodes of depression and hypomania. Therefore, the main distinction between the 2 types is the severity of manic symptoms: full mania causes severe functional impairment, can include symptoms of psychosis, and often requires hospitalization; hypomania, by contrast, is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization.[3]

Longitudinal studies show that patients with bipolar disorder of either type experience symptomatic depression at least 3 times more frequently than symptomatic mania or hypomania (**Figure 1**).[4-9] The lifetime prevalence of bipolar disorder in adults in the United States is reported to be 3.9%.[10]

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KEY POINTS

➤ Bipolar disorder is a dynamic and serious condition that can have a lifelong impact on a patient's overall health status, quality of life, and functioning.

➤ The treatment of bipolar disorder is challenging and costs the US healthcare system an estimated >$30 billion in direct expenditures and >$120 billion in indirect costs annually.

➤ Delayed diagnosis can result in worsening clinical outcomes and increased costs; early recognition of this condition can reduce the total per-patient costs by as much as $2316 annually.

➤ Considering the possibility of bipolar disorder in patients with depressive disorders is critical to improving outcomes and reducing costs of treatment.

➤ Despite the introduction of new therapies for bipolar disorder, treatment outcomes remain less successful than for major depressive disorder; the use of antidepressants for this condition remains controversial.

➤ Medication nonadherence is perhaps the most significant contributor to poor outcomes in this patient population; monotherapy may help improve adherence in some patients.

➤ The selection of an appropriate treatment that takes into account efficacy as well as safety can help to ameliorate the devastating impact of bipolar disorder.
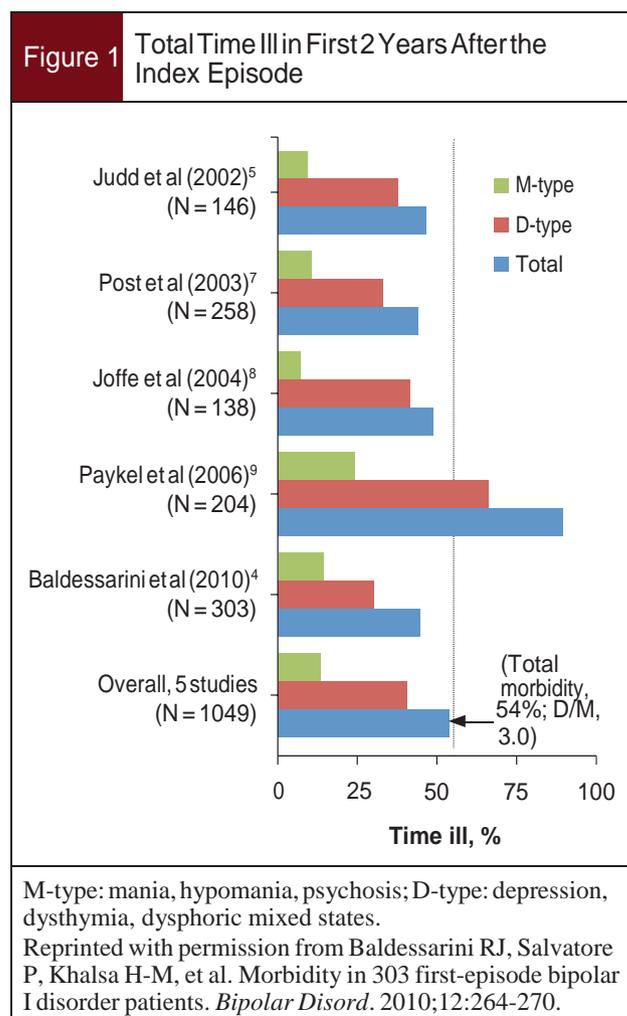
Bipolar disorder has an enormous economic impact on the US healthcare system.[11,12] The estimated total direct cost of bipolar disorder (including inpatient costs, outpatient costs, pharmaceuticals, and community care) in the United States in 2009 was $30.7 billion.[11] In addition, the adverse impact of bipolar disorder on functioning and quality of life translates to a substantial total indirect healthcare cost resulting from the loss of employment, loss of productivity, sick leave,[13] and uncompensated care that is estimated at more than $120 billion annually.[11]

From a managed care perspective, bipolar disorder is among the most costly of all mental health conditions. In a major study of commercial insurance claims data from 1996 of almost 1.7 million individuals, although only 3% of patients with a mental health claim were identified with bipolar disorder, these patients accounted for 12.4% of the total plan expenditures.[14] High cost was driven largely by a disproportionate rate of inpatient admissions for bipolar disorder versus all other behavioral health claimants (39.1% vs 4.5%, respectively), resulting in a cost of $1.80 for inpatient care per

every dollar of outpatient treatment cost.[14]

Another large study of healthcare utilization and costs from 2004 to 2007 compared 122 patients with bipolar disorder with patients with other psychiatric conditions, including 1290 patients with depression, 2770 with asthma, 1759 with coronary artery disease, and 1418 with diabetes.[12] The patients with bipolar disorder had higher adjusted mean costs per member per month (approximately $1700) than all other groups, including depression (approximately $1300), with the exception of patients who had both diabetes and coronary artery disease (with approximately $2000 per member per month).[12]

Despite the advent of lithium therapy more than 60 years ago,[15] the introduction of other pharmacotherapies and the development of disease-specific behavioral approaches,[16] and a generally greater awareness of bipolar disorder, treatment outcomes remain less satisfactory than the outcomes for major depressive disorder (MDD) in all sectors of the US healthcare system, including

Figure 1 Total Time Ill in First 2 Years After the Index Episode

M-type: mania, hypomania, psychosis; D-type: depression, dysthymia, dysphoric mixed states.
Reprinted with permission from Baldessarini RJ, Salvatore P, Khalsa H-M, et al. Morbidity in 303 first-episode bipolar I disorder patients. *Bipolar Disord*. 2010;12:264-270.

managed care.[2] This represents a challenge and an opportunity for managed care to focus on this disorder to improve outcomes and to reduce healthcare costs.

This review article presents the clinical evidence supporting best practice for the diagnosis and treatment of bipolar disorder. The review highlights what little is known about the most effective ways to address specific clinical challenges in caring for patients with bipolar disorder and identifies recent research that documents innovative approaches to improving the effectiveness of care in this setting.

Study Selection Methodology

Studies were selected for inclusion in this review based on a comprehensive literature search initially using MEDLINE/PubMed and Google Scholar, and was restricted to the years 1994 to the present. The search terms included "bipolar disorder," "mania," "bipolar depression," "mood stabilizer," "atypical antipsychotics," and "antidepressants." For the sections on diagnosis, treatment, and key challenges, articles were selected for inclusion from the extensive literature based on the clinical judgment of the author, using the conventional criteria of relevance, importance, and robustness of data. In selecting studies for inclusion, a broad representation of topics was sought, while limiting the total number of references on any given topic; high-quality, recent reviews of major topics were included to supplement the primary studies.

Diagnosis

A diagnosis of bipolar disorder is obvious when a patient presents with florid mania but is challenging when the initial presentation includes depressive symptoms; studies generally report that 50% or more of patients initially present with depression.[3,17-20] Primarily because unipolar depression (ie, MDD) is more common than bipolar depression, and because bipolar depression lacks pathognomonic features, bipolar disorder is often incorrectly identified as MDD.[21] Among patients who are eventually diagnosed with bipolar disorder, approximately 70% reportedly had an initial misdiagnosis and more than 33% remained misdiagnosed for 10 years or more.[22] Delay in diagnosis is a particular problem in women with bipolar disorder type II, because the symptoms of hypomania may not be very apparent.[23] Moreover, misdiagnosis during the postpartum period is common; in a study of 56 women referred for postpartum depression, 54% were later rediagnosed with bipolar disorder.[24]

The delayed recognition of bipolar disorder has adverse clinical and healthcare cost consequences.[21,25,26] From a clinical perspective, patients with bipolar disor-der who are treated with antidepressants alone (the standard of care for MDD) are less likely to have an appropriate response and are at risk for manic switch or cycle acceleration (ie, increased frequency of mood episodes over time).[27,28]

From a health economic perspective, care is likely to be more costly in patients with delayed diagnosis of bipolar disorder than in those diagnosed early. In an analysis from the California Medicaid program, 2 groups of patients with bipolar disorder were compared: those who were diagnosed with bipolar disorder at initial presentation and those who had a delayed diagnosis during a 6-year follow-up.[26] Patients with a delayed diagnosis of bipolar disorder represented almost twice as many cases as those with initially recognized bipolar disorder (28.2% vs 14.5%, respectively), and the annualized total cost per patient in the delayed group was $2316 higher in the sixth year compared with the cost for patients whose disease was initially recognized as bipolar disorder ($P <.001$). Moreover, costs for patients with bipolar disorder and a delayed diagnosis increased by $10 monthly before the correct diagnosis ($P <.001$) and decreased by $1 afterward ($P = .006$ for the change in slope).[26] Thus, the consideration of the possibility of bipolar disorder in patients with depressive disorders is critical to improving outcomes and reducing the costs of care of patients with bipolar disorder.

Screening each patient for a history of mania and hypomania on their initial presentation of depressive symptoms is an early step toward the recognition of bipolar disorder.[29] Validated instruments that can be used include the Mood Disorder Questionnaire,[30] the Composite International Diagnostic Interview, version 3.0,[31] and the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire.[32] Clinical screening can be supplemented with electronic health record (EHR)-based case findings, in which information collected by self-report or a healthcare assistant is entered into the EHR and is screened for possible indicators of bipolar disorder.[33]

These tools help to ensure that the clinician recognizes patients who are more likely to have bipolar disorder, help assist in directing the clinical interview, and can encourage active follow-up for any emerging symptoms of bipolar disorder. In a study modeling the clinical outcome and cost-effectiveness over 5 years of administering the Mood Disorder Questionnaire to all patients first presenting with symptoms of MDD, screening resulted in an increase in diagnostic accuracy for bipolar disorder, with an additional 38 cases identified per 1000 patients screened and a per-patient savings of $1937, for a total annual budgetary savings of more than $1.9 million.[34]

Pharmacologic Treatment

Pharmacologic treatments for bipolar disorder include the conventional mood stabilizers (eg, lithium, valproate, lamotrigine, and carbamazepine) and most of the currently marketed atypical antipsychotics.[2,21] A detailed review of randomized controlled trials (RCTs) and observational studies for every agent in the treatment of each of the phases of bipolar disorder is beyond the scope of this review; rather, a summary of the most important findings of the aggregated evidence is presented from systematic reviews and meta-analyses,[15,35] as well as the results of recent studies that address previous gaps in the literature.[36,37]

It is relevant to note that the level of trial evidence varies for the different pharmacotherapies that are approved for the treatment of bipolar disorder. Some of these agents have evidence of efficacy in acute mania, others in acute bipolar depression, and a limited number of therapies have efficacy at both poles of the disease spectrum. Some therapies demonstrate efficacy only in acute episodes, whereas others show efficacy as maintenance therapy.

Mood Stabilizers

Lithium has been the foundation of treatment of bipolar disorder for over 60 years,[2,15,38] but its efficacy in the prevention and treatment of bipolar depression is limited, and it is not rapidly effective for acute mania.[15] In a systematic review of RCTs with a lithium arm that were published between 1970 and 2006, lithium had a significant prophylactic effect for all relapses (random effects relative risk [RR], 0.65; 95% confidence interval [CI], 0.50-0.84) and manic relapses (RR, 0.62; 95% CI, 0.40-0.95) but not for depressive relapses (RR, 0.72; 95% CI, 0.49-1.07).[15] Notably, lithium remains the only agent proved to reduce the risk for suicide in patients with bipolar disorder.[39]

Sodium valproate is the most frequently used antiepileptic mood stabilizer for patients with bipolar disorder. In the BALANCE trial, a 2-year active controlled trial, 330 patients were receiving maintenance therapy with lithium or valproate, or the combination of both; the primary outcome was time to first mood episode.[40] Although the combination performed best, lithium was more effective than valproate alone (hazard ratio [HR] for the primary outcome, 0.71; 95% CI, 0.51-1.00; P = .047).[40]

A nationwide observational study conducted in Denmark from 1995 to 2006 of 4268 patients who received lithium or valproate for the treatment of bipolar disorder found a higher rate of adding medications or switching to another drug among patients receiving valproate compared with lithium (HR, 1.86; 95% CI, 1.59-2.16) and a higher rate of hospitalization (HR, 1.33; 95% CI, 1.18-1.48).[41]

Lamotrigine is the mood stabilizer with the best evidence for bipolar depression prophylaxis.[28] Published data on the use of lamotrigine for acute depression in patients with bipolar disorder are inconsistent, but a meta-analysis did find significant efficacy for a higher dose of 200 mg/day.[28,42]

Each of the mood stabilizers presents significant safety issues. Lithium has a narrow therapeutic window that leads to the requirement for regular monitoring of serum concentrations; it can be fatal in overdose, and is associated with progressive renal insufficiency and hypothyroidism.[21,43] Valproate is associated with hepatotoxicity, whereas lamotrigine is linked with rash and Stevens-Johnson–like syndrome.[21,44,45] Valproate and lithium are both teratogenic.[46]

Atypical Antipsychotics

A vast body of evidence supports the use of atypical antipsychotics in the treatment of bipolar disorder.[35] The most established role for this class is in the treatment of acute mania. All approved atypical antipsychotics (with the exception of lurasidone) have been shown to be effective in the treatment of manic episodes of bipolar disorder I.[35] In contrast, only quetiapine (immediate-release and extended-release formulations) has the highest level (level 1) of evidence for efficacy as monotherapy for bipolar I or II depression.[35] More recently, quetiapine was also shown to reduce the symptoms of depression in acute mixed episodes of bipolar II hypomania.[36] One single trial of the combination agent of olanzapine and fluoxetine shows the efficacy of this agent in bipolar I depression[28]; lurasidone was approved in 2013 by the US Food and Drug Administration (FDA) for the treatment of adults with bipolar I depression.[47] Other atypical antipsychotics, including aripiprazole, have not shown efficacy in trials of patients with bipolar depression.[48]

The safety and tolerability of atypical antipsychotics are well characterized in the literature.[49,50] The adverse effects of atypical antipsychotics differ between individual agents. In a meta-analysis of 48 RCTs in which at least 2 atypical antipsychotics were compared and risperidone served as the index medication, weight gain was significantly increased with olanzapine (odds ratio [OR], 2.139; 95% CI, 1.764-2.626) and was decreased with ziprasidone (OR, 0.466; 95% CI, 0.317-0.657); extrapyramidal symptoms were decreased with quetiapine (OR, 0.441; 95% CI, 0.129-0.910).[50]

Atypical antipsychotics as a class have a propensity to contribute to metabolic risk in patients with bipolar disorder, and monitoring strategies have been proposed to prevent, minimize, or detect symptoms early so that appropriate measures can be taken.[49]

Table	Guideline Recommendations for the First-Line Treatment of Bipolar Disorder

Guideline	Acute treatment			Maintenance	
VAD/DoD (2010)[54]	**Mania**	**Bipolar depression**	**Mixed states**	**Mania**	**Depression**
	Lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone	Quetiapine, lamotrigine, lithium	Valproate, carbamazepine, olanzapine, aripiprazole, risperidone, ziprasidone	Agent effective in acute phase; monotherapy advised Lithium, olanzapine; lithium/valproate + quetiapine	Agent effective in acute phase; monotherapy advised Lithium, lamotrigine; lithium/valproate + quetiapine
WFSBP (2009, 2010, 2013)[55-57]	Aripiprazole, risperidone, valproate, ziprasidone	Bipolar I depression	Bipolar II depression	No specific recommendations	Mania	Depression	Any episode
		Quetiapine	Quetiapine, lithium/valproate + pramipexole, valproate, antidepressants		Aripiprazole, lithium, quetiapine	Lamotrigine, quetiapine	Aripiprazole, lamotrigine, lithium, quetiapine
CANMAT (2013)[38]	Lithium, valproate, aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone, ziprasidone, asenapine, paliperidone XR, lithium/valproate + aripiprazole, lithium/valproate + olanzapine, lithium/valproate + quetiapine, lithium/valproate + risperidone, lithium/valproate + asenapine	Bipolar I depression	Bipolar II depression	No specific recommendations	Bipolar I disorder	Bipolar II disorder
		Lithium, lamotrigine, quetiapine, quetiapine XR, lithium/valproate + SSRI, olanzapine + SSRI, lithium + valproate, lithium/valproate + bupropion	Quetiapine, quetiapine XR		Lithium, lamotrigine (limited efficacy in preventing mania), quetiapine, risperidone LAI, aripiprazole, lithium/valproate + quetiapine, lithium/valproate + risperidone, LAI lithium/valproate + aripiprazole or lithium/valproate + ziprasidone	Lithium, lamotrigine, quetiapine
BAP (2009)[52]	Mild: lithium, carbamazepine Severe: antipsychotic, valproate	Bipolar depression		Mild: lithium, carbamazepine Severe: antipsychotic, valproate	Mania	Depression
		Quetiapine, lamotrigine, SSRI or other antidepressant (not TCA)			Lithium, aripiprazole, quetiapine, valproate, olanzapine	Quetiapine, lamotrigine
APA (2002)[21]	Severely ill: lithium/valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Severely ill: lithium/valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Lithium, lamotrigine	Severely ill: lithium/valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Lithium, valproate, carbamazepine, oxcarbazepine	

LAI indicates long-acting injection; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XR, extended release.

Antidepressants

The use of antidepressants as pharmacotherapy for bipolar disorder is the area of greatest controversy related to this disease.[27,51] In a random-effects meta-analysis of 10 studies that included 2226 patients with unipolar depression and 863 patients with bipolar disorder, antidepressant responses did not differ between the 2 groups (pooled RR, 1.05; 95% CI, 0.96-1.15; $P = .34$).[51] However, the risk rate for a switch to mania was 2.5% weekly in patients with bipolar depression compared with 0.28% in patients with unipolar depression.

Antidepressants are not FDA-approved for the treatment of bipolar disorder, with the exception of fluoxetine in combination with olanzapine, although antidepressants are frequently prescribed in clinical practice for the depressive symptoms of bipolar disorder.

The current guidelines[21,38,52] are generally consistent in making the recommendations listed in the **Table** regarding antidepressant use in bipolar depression, indicating that selective serotonin reuptake inhibitors

(other than paroxetine) and bupropion may be used as first-line treatments in patients with bipolar disorder with no history of rapid cycling and without concomitant manic symptoms, but always in conjunction with a mood stabilizer or an atypical antipsychotic. Antidepressants should be tapered and discontinued after full remission of depression; the role of antidepressants in maintenance treatment is unclear.[27,28]

Treatment Guidelines

Treatment guidelines are a critical source for the rational pharmacotherapy of bipolar disorder.[21,52] The American Psychiatric Association guidelines for bipolar disorder have not been updated since 2002, and therefore do not include data that became available more recently.[21] In a systematic overview of the current international guidelines for bipolar disorder conducted in 2011, the recommendations with the greatest degree of consensus and best evidence for first-line treatment were the use of (1) lithium, divalproex, or an atypical
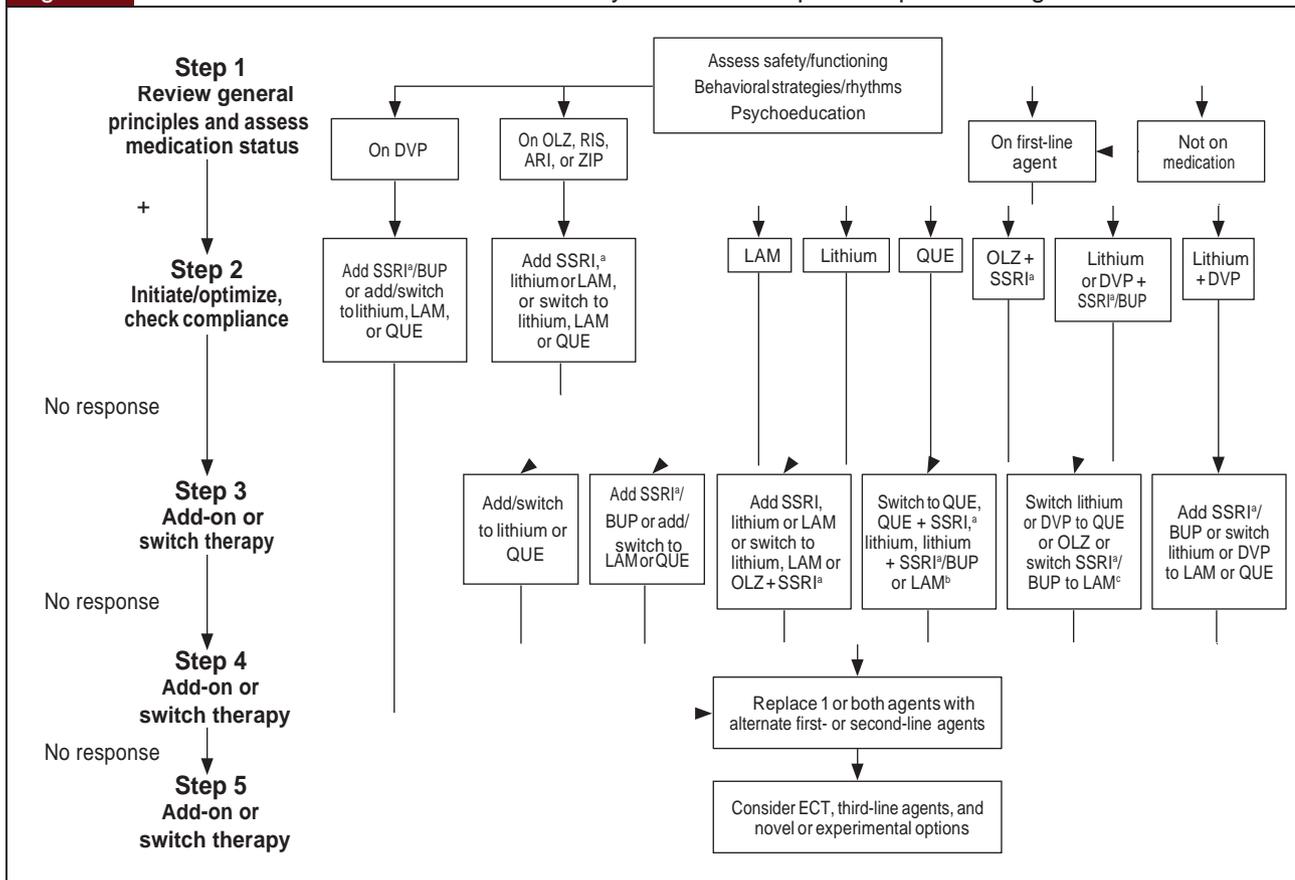

Figure 2A Canadian Network for Mood and Anxiety Treatments Mania Algorithm
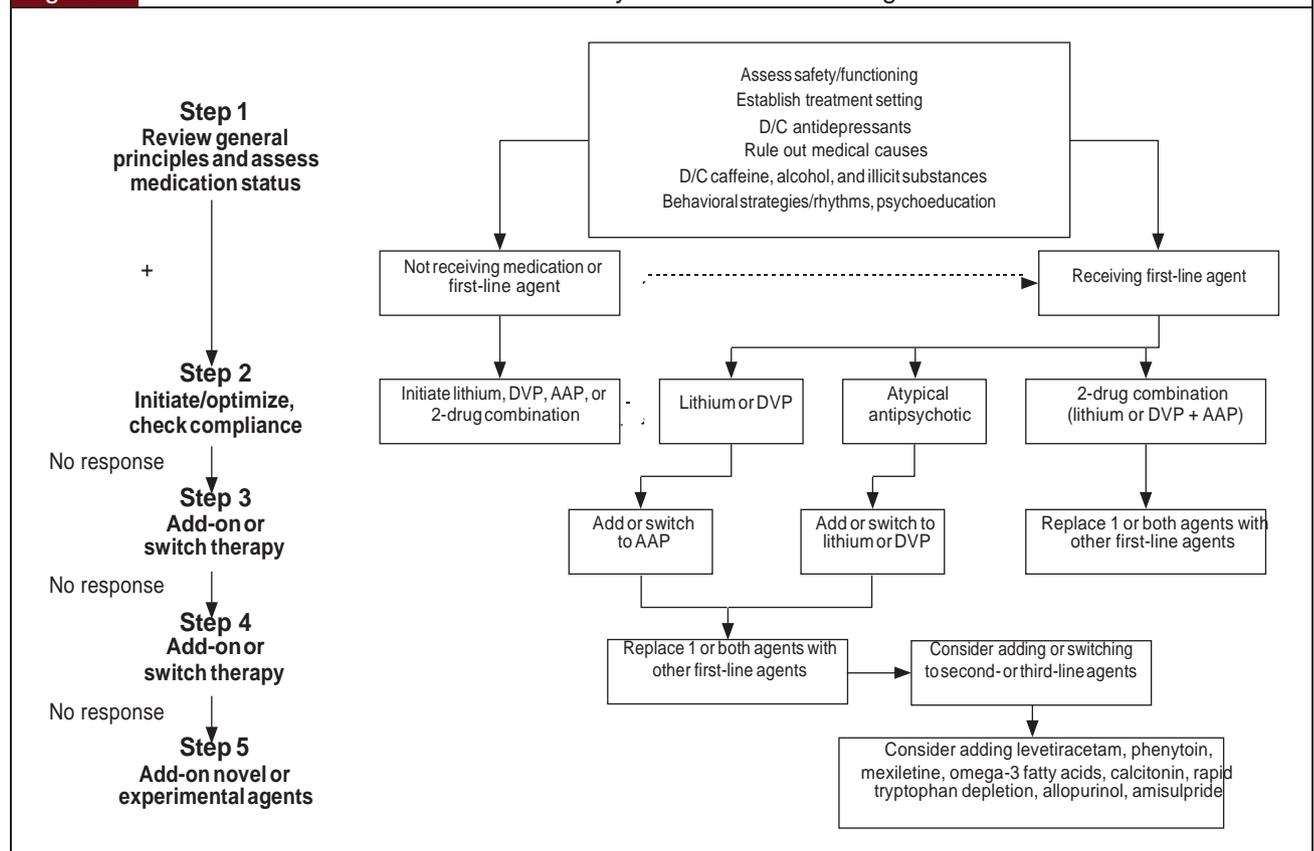
AAP indicates atypical antipsychotic; D/C, discontinue; DVP, divalproex.
Reprinted with permission from Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15:1-44.

Figure 2B Canadian Network for Mood and Anxiety Treatments Bipolar Depression Algorithm

aExcept paroxetine.

bOr switch the SSRI to another SSRI.

cOr switch the SSRI or BUP to another SSRI or BUP.

ARI indicates aripiprazole; BUP, bupropion; DVP, divalproex; ECT, electroconvulsive therapy; LAM, lamotrigine; OLZ, olanzapine; QUE, quetiapine; RIS, risperidone; SSRI, selective serotonin reuptake inhibitor; ZIP, ziprasidone.
Reprinted with permission from Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15:1-44.

antipsychotic, for acute mania; (2) divalproex or an atypical antipsychotic, for mixed episodes (ie, manic and depressed symptoms together); (3) quetiapine, olanzapine/fluoxetine combination, or lamotrigine, for bipolar depression; and (4) group or individual psychological education should be offered to all patients with bipolar disorder.[53]

The Table provides a summary of first-line pharmacotherapy recommendations from a selected set of comprehensive guidelines.[21,38,52,54-57] However, implementation of the guidance in any treatment algorithm for bipolar disorder is challenging, because of the multiple factors involved in drug selection, drug interactions, adverse side effects, and patient adherence (**Figure 2A** and **Figure 2B**).[38]

Major Challenges in the Treatment of Bipolar Disorder

In addition to the importance of implementing an expeditious diagnosis, evidence-based prescribing, and cost-effective therapies, other challenges must be recognized and addressed in the treatment of patients with bipolar disorder to improve treatment outcome.

Treatment Nonadherence

Nonadherence to treatment is perhaps the most significant contributing factor to poor outcome in patients with bipolar disorder.[58,59] Medication possession ratio (MPR) has been used to assess treatment adherence. MPR is the ratio of the number of days that an antipsychotic medication, for example, was filled

compared with the total number of days during the follow-up period. An MPR of 1 indicates that for a medication prescribed for a patient over a given time, prescriptions were filled 100% of that period. A priori MPR percentage thresholds of 70% to 80% have been set to define adherence versus nonadherence; a threshold of 75% or 80% represents a level of adherence that is associated with better outcomes in patients with bipolar disorder.[58-61]

In one study with 1973 commercially insured patients, the mean MPR was only 0.46 (SD, ±0.32); patients whose MPR was ≥0.75 had a lower risk for all-cause rehospitalization (OR, 0.73; 95% CI, 0.58-0.92) and mental health–related rehospitalization (OR, 0.76; 95% CI, 0.60-0.96).[58] Similarly, among 1399 commercially insured patients, reduced adherence (<80%) to traditional mood-stabilizing therapy was associated with a greater risk for emergency department visits (OR, 1.98; 95% CI, 1.38-2.84) and inpatient hospitalizations (OR, 1.71; 95% CI, 1.27-2.32).[59]

In one of the largest studies of its type, using claims data from the 2000-2006 PharMetrics database (a large US database of commercial health plans), 78.7% of the 7769 patients with bipolar disorder had an MPR <0.75. An MPR ≥0.80 was associated with a reduction in risk for mental health–related hospitalization (OR, 0.82; 95% CI, 0.70-0.95), and an MPR ≥0.90 was also associated with a reduction in the risk for a mental health–related emergency department visit (OR, 0.71; 95% CI, 0.54-0.91).[60] Similar findings have been reported in Medicaid-insured populations.[61]

Because adherence tends to worsen with the addition of each medication to a pharmacotherapeutic regimen, monotherapy may be considered a practical option in patients with poor adherence.[62,63]

Psychiatric Comorbidities

Patients with bipolar disorder are predisposed to other comorbid psychiatric disorders at higher rates than patients with other psychiatric disorders.[64,65] Anxiety disorders and alcohol or drug dependence are particularly common comorbidities, with major consequences for treatment outcome and increased cost.[64,66] Comorbidity is the rule rather than the exception in bipolar disorder,[64,65] with approximately 66% of patients having 1 comorbid mental health diagnosis and approximately 66% having 2 other conditions.[66]

These comorbid psychiatric conditions are associated with longer episodes of bipolar illness[64,66]; shorter time in remission (ie, euthymia)[64,66]; polypharmacy, with the potential for drug interactions[67]; and an increase in related problems, such as poor treatment compliance and suicidality.[65]

General Medical Comorbidities

Patients with bipolar disorder also have a high rate of other medical comorbidities, including diabetes, cardiovascular disease, obesity, migraine, and hepatitis C virus (HCV) infection.[66,68] In a Veterans Administration (VA) study, patients with bipolar disorder had a higher prevalence of diabetes than patients in a national VA cohort (17.2% vs 15.6%, respectively; P = .0035) and of HCV (5.9% vs 1.1%, respectively; P <.001).[68] Several reasons can potentially account for this increased burden of medical illness, including shared biologic predisposition (eg, migraine), comorbid substance misuse (HCV), as well as adverse effects of treatment (obesity and diabetes).[69] Not surprisingly, medical comorbidities are associated with a significant increase in the total cost of care.[70,71]

Suicide

Suicide is more frequent among patients with bipolar disorder than among patients with any other psychiatric or general medical disorder.[72,73] Suicide among patients with bipolar disorder is estimated to occur at an annual rate of 0.4% (1 for every 250 individuals with bipolar disorder), which is more than 20 times than in the general US population.[73] In the Epidemiologic Catchment Area database, which is still one of the best US databases regarding the epidemiology of psychiatric disorders, the lifetime rate of suicide attempts for persons with bipolar disorder was 29.2%—almost twice the rates of MDD (15.9%) and other *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*–defined Axis I disorder (4.2%).[72]

Suicide attempts are very costly.[74] In a study using data from the PharMetrics Integrated Outcomes Database (1995-2005), the total costs for 352 patients with bipolar disorder who attempted suicide were compared between the years after and before the first suicide attempt. The mean healthcare cost for the 1 year after the suicide attempt was $25,012 versus $11,476 for the 1 year before (P <.001). During the month after the suicide attempt, a large increase was reported in inpatient and emergency services, followed by enduring long-term increases in medication and outpatient costs.[74]