REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Bipolar Disorder

Andre F. Carvalho, M.D., Ph.D., Joseph Firth, Ph.D., and Eduard Vieta, M.D., Ph.D.

From the Department of Psychiatry, University of Toronto, and the Centre for Addiction and Mental Health, Toronto (A.F.C.); the IMPACT (Innovation in Mental and Physical Health and Clinical Treatment) Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, VIC (A.F.C.), and the NICM Health Research Institute, Western Sydney University, Westmead, NSW (J.F.) — both in Australia; the Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, United Kingdom (J.F.); and the Psychiatry and Psychology Department of the Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS (August Pi i Sunyer Biomedical Research Institute), and CIBERSAM (Biomedical Research Networking Center for Mental Health Network), Barcelona (E.V.). Address reprint requests to Dr. Carvalho at the Centre for Addiction and Mental Health, Bell Gateway Bldg. 100 Stokes St., 4th Fl., Toronto ON M6J 1H4, Canada, or at andrefc7@hotmail.com.

This article was updated on July 2, 2020, at NEJM.org.

N Engl J Med 2020;383:58-66.
DOI: 10.1056/NEJMra1906193

Mood fluctuations are common during normal daily life as a result of either stressful or pleasant events. However, severe and persistent mood swings that result in psychological distress and behavioral impairment may be symptomatic of an underlying affective disorder. Affective disorders are classified along a spectrum from unipolar depressive disorders to bipolar disorder types II and I.[1]

Bipolar disorder as a distinct entity was described by Falret in the 1850s.[2] The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), includes the category "bipolar and related disorders," which encompasses bipolar II, bipolar I, and cyclothymic disorders. Atypical bipolar-like phenomena that do not fit the canonical subtypes are included in the "other specified and bipolar related disorder" category.[3] The recently released *International Classification of Diseases*, 11th Revision (ICD-11), also includes a section on bipolar disorders.[4]

The main characteristic separating bipolar disorders from other affective disorders is the presence of recurring manic or hypomanic episodes that may alternate with depressive episodes. Bipolar I disorder is defined by the presence of overt manic episodes with a range of manifestations, including overconfidence, grandiosity, talkativeness, extreme disinhibition, irritability, decreased need for sleep, and highly elevated mood. Psychotic symptoms such as delusions and hallucinations occur in up to 75% of manic episodes, and episodes of any severity may compromise psychosocial functioning to the point that hospitalization is required. Bipolar II disorder is characterized mainly by episodes of depression but alternating with hypomania rather than mania. The presence of at least one hypomanic episode in a life trajectory is considered to be consistent with the diagnosis of bipolar II disorder. Cyclothymic disorder is characterized by recurring depressive and hypomanic states, lasting for at least 2 years, that do not meet the diagnostic threshold for a major affective episode.

During periods of heightened mood, persons with bipolar disorder may also be paradoxically affected by depressive symptoms. According to the DSM-5, symptoms must be present for at least 1 week for a diagnosis of a manic episode to be made, or 2 weeks for diagnosis of a depressive episode. However, those durations are arbitrary and have no biologic basis.

The onset of bipolar disorder typically occurs at around the age of 20 years. An earlier onset is often associated with a poorer prognosis, longer treatment delays, more severe depressive episodes, and higher prevalences of concurrent anxiety and substance use disorders.[5] The first episode of bipolar disorder is usually depressive, and for most persons with either bipolar I or bipolar II disorder, depressive episodes last considerably longer than manic or hypomanic episodes throughout the course of illness. For this reason, bipolar disorder is often misclassified as major depressive disorder.[6] However, there is also evidence that bipolar disorder

may be overdiagnosed in some circumstances,[6] particularly when clinicians rely solely on self-reported screening instruments, since there is evidence that screening tools have high false positive rates for the diagnosis of bipolar disorder.[7] In up to a third of affected persons, bipolar disorder is not diagnosed until 10 years after the onset of symptoms.[8]

EPIDEMIOLOGY AND BURDEN OF ILLNESS

Bipolar disorders rank as the 17th leading source of disability among all diseases worldwide.[9] The World Mental Health Survey Initiative reported lifetime and 12-month prevalence estimates for bipolar disorders of 2.4% and 1.5%, respectively.[10] Prevalence rates vary by country, perhaps because of methodologic issues and cultural differences. For instance, a systematic review and meta-analysis showed a 0.11% lifetime prevalence rate for bipolar disorder in China.[11] The prevalence of bipolar I disorder is similar for males and females, whereas bipolar II disorder occurs more frequently among females. Bipolar disorder is prevalent in primary care practices. For example, a study showed that up to 9.8% of primary care patients at one large group practice in New York City had a positive screening test for bipolar disorder, which appeared to have been underrecognized and undertreated,[12] and another study showed that 15% of patients receiving care for unipolar depression in primary care practices may have an unrecognized bipolar disorder.[13]

Several nonpsychiatric medical and sociological conditions have been identified as possible risk factors for bipolar disorder in observational studies, although few of these findings are supported by high-quality evidence. For example, a recent review showed tentative associations among irritable bowel syndrome, adversity in childhood, and bipolar disorder.[14]

Since bipolar disorder typically first arises during the formative years in children and adolescents, achievement of developmental, educational, and occupational milestones is often adversely affected. Cognitive and psychosocial dysfunction during acute episodes or in periods of remission compounds the problem.[15]

Approximately 6 to 7% of persons with bipolar disorder commit suicide; there is evidence that suicide rates among persons with bipolar disorder are 20 to 30 times as high as the rates in the general population.[16] Several sociodemographic and clinical factors may aid in stratifying the risk for suicide among patients with bipolar disorder[16,17] (Table 1).

Table 1. Risk Factors for Suicide Attempts and Deaths Due to Suicide among Persons with Bipolar Disorder.

Risk Factors for Suicide Attempts	Risk Factors for Death Due to Suicide
Female sex	Male sex
Younger or older age	Older age
Minority race or ethnic background (youth only)	
Residence in middle-income countries	
Bipolar I disorder	
Residence in the Americas	
Single or divorced marital status, single parent	
Predominant depressive polarity*	
Depressive or mixed index episode	Depressive or mixed index episode or manic index episode with psychotic symptoms
Other characteristics of episodes (mixed features, greater number or severity of episodes, rapid cycling, anxiety, atypical features, suicidal ideation)	Other characteristics of episodes (hopelessness, psychomotor agitation)
Coexisting psychiatric conditions (substance use disorder, anxiety disorder, eating disorder, borderline and other personality disorders)	Coexisting anxiety disorder
Cigarette smoking, coffee consumption	
Obesity and overweight	
First-degree relative with mood disorders, suicide	First-degree relative with mood disorders, suicide
Prior suicide attempts	Prior suicide attempts
Early-life trauma (childhood maltreatment)	
Interpersonal conflicts, occupational problems, bereavement, social isolation	Interpersonal conflicts, occupational problems, bereavement, or social isolation present within 1 wk before death
Sexual dysfunction	

* A predominance of either depressive or manic polarity (predominant polarity) is found in approximately half of patients with bipolar disorder.[18]

Persons with bipolar disorder have high rates of coexisting psychiatric conditions, including anxiety (estimated to be present in 71% of persons with bipolar disorder), substance use (in 56%), personality disorders (in 36%), and atten-

tion deficit–hyperactivity disorder (in 10 to 20%). When these additional problems are present, they increase the burden of illness and worsen the prognosis. Targeted interventions for these concurrent conditions have been suggested.[19,20] However, high rates of coexisting mental disorders may also reflect the failure of our current diagnostic systems to capture an individual patient's overall mental health.[21]

Also more prevalent among persons with bipolar disorder than in the general population are chronic medical conditions such as metabolic syndrome (affecting 37% of patients with bipolar disorder),[22] migraine (35%),[23] obesity (21%),[19] and type 2 diabetes mellitus (14%).[24] As compared with the general population, persons with bipolar disorder have approximately twice the risk of death,[25] which is attributable to both suicide and higher rates of physical diseases in this population.[26,27] Monitoring and interventions for physical health conditions among patients with bipolar disorder have been suggested by a recent commission.[28]

GENETIC AND NEUROBIOLOGIC FEATURES

Estimates of heritability for bipolar disorder range from 70 to 90%.[29] Tentative findings regarding the underlying genetics and potential neurobiologic pathways of bipolar disorders have been derived from genomewide association studies. Many genes with small effect sizes are considered to contribute to the group of disorders. For example, a genomewide association study in 2019 identified 30 significant loci, of which 20 had not previously been recognized.[30] A pathway analysis showed enriched gene sets in bipolar populations, including sets involved in the regulation of insulin secretion and endocannabinoid signaling. However, those common variants of risk altogether account for only approximately 25% of the overall heritability of the disorder.[29] Furthermore, common genetic variants are thought to interact with environmental risk factors, but the latter are also not well established.[31]

A "kindling" hypothesis has been postulated as a model to explain gradual stress sensitization that leads to recurring affective episodes. In this model, the first episode of bipolar disorder occurs after exposure to a stressor, and subsequent episodes can occur without exposure to an identifiable stressful event. The mechanisms underpinning the kindling hypothesis may be strengthened if the illness is not treated or if the person is exposed to psychoactive substances or has lifestyle risks such as smoking or sedentary behavior, both of which occur more frequently among persons with bipolar disorder than in the general population.[28] Poorly characterized epigenetic mechanisms are also considered to contribute to the putative kindling phenomenon.[32]

Progressive changes in brain structure and cellular function, referred to as neuroprogression, have been observed in some studies of recurrent episodes of affective disorder .[33] A long duration of illness has been associated with reduced cortical thickness of such brain regions as the prefrontal cortex, which may play a role in stress regulation.[34] Epigenetic mechanisms,[32] deregulation of mitochondrial function, pathways subserving neuroplasticity, inflammation, and an increase in oxidative and nitrosative stress have all been proposed as factors that promote neuroprogression within the context of bipolar disorder.[33] Aberrations in the hypothalamic–pituitary–adrenal axis are also thought to play a major role in the pathophysiology and progression of bipolar disorder.[35] Neuroprogression may account for worsening cognitive and functional impairments.[36] The mechanisms underpinning neuroprogression may also contribute to a higher prevalence of coexisting medical conditions, as well as premature death among persons with bipolar disorder.[37] For example, the prevalence of type 2 diabetes mellitus is higher among persons with multiepisode bipolar disorder than among those with single-episode bipolar disorder.[24] Finally, some evidence indicates that as bipolar illness progresses, the response to mood-stabilizing medications may decrease.[36] However, the courses and trajectories of bipolar disorder are heterogeneous, and a subgroup of patients preserves cognitive and psychosocial functioning and productivity throughout the illness.[38]

MANAGEMENT

GENERAL PRINCIPLES

Most patients with bipolar disorder initially seek help from a primary care clinician. A meta-

analysis has shown that collaborative care models used in primary care practice improve both mental and physical health outcomes among people with mental illnesses, including bipolar disorder.[39]

Medical and psychiatric conditions that mimic affective episodes should be ruled out during diagnostic assessment for an affective disorder. For instance, substance use disorders and psychotic disorders such as schizoaffective disorder are part of the differential diagnosis for bipolar disorder because they can be manifested as episodic psychotic disturbances. In addition, the early phases of frontotemporal dementia, neurosyphilis, hypothyroidism, fatigue from anemia, and congestive heart failure, as well as specific antineural antibody syndromes, are part of the differential diagnosis for bipolar disorders in appropriate cases, particularly at the first presentation.

Several factors influence the selection of initial treatment, including patients' preference, coexisting medical and psychiatric conditions, and previous responses to treatment, including associated side effects. During acute affective episodes, the safety of patients should be ensured, particularly by determining whether they are at risk for suicide or aggression toward themselves or others and, if so, introducing measures to reduce the risk. It is advisable to discuss evidence-based pharmacologic and nonpharmacologic interventions with patients and to monitor adherence to the extent that is possible. Finally, the definition of treatment-resistant bipolar disorder is a matter of debate, and clinical judgment is used to determine when the disorder is not controlled by medications. However, operational definitions have been proposed by expert panels.[40,41]

TREATMENT OF ACUTE EPISODES

Acute Mania

Pharmacologic treatment with antipsychotic agents or mood stabilizers is the mainstay of treatment for acute mania and hypomania. Nonpharmacologic strategies may also be used for patients with treatment-resistant or severe mania. There is minimal evidence regarding the choice of medication for hypomania, and treatments for mania are often used for hypomanic episodes. The mood stabilizers and antipsychotic agents approved by the Food and Drug Administration (FDA) for the management of bipolar disorder are listed in Table 2. Meaningful differences in efficacy among these treatments have not been observed in head-to-head trials. Network meta-analyses have suggested some differences in efficacy — specifically, risperidone was more effective than aripiprazole and more effective than valproate in some analyses.[42,43] The safety profiles of the various antimanic treatments and their acceptability to patients vary (Table 2).[42,43]

For patients with acute mania, if there is no response to a medication after 1 to 2 weeks, a different medication may be considered. The combination of an antipsychotic agent and a mood stabilizer, especially for severe mania, appears to be more efficacious than either medication alone.[44] In a trial involving children, the antipsychotic agent risperidone was more effective than lithium or divalproex sodium. However, the higher efficacy of such treatment approaches must be weighed against their metabolic adverse effects, especially with atypical (second-generation) antipsychotic agents (e.g., risperidone) in both children and adults.[45]

Other antipsychotic agents have been effective in the management of acute mania — for example, haloperidol and paliperidone. However, these drugs have not been approved by the FDA for this indication. Bifrontal electroconvulsive therapy (ECT), either as monotherapy or as an adjunctive treatment, has been reported to be effective for patients with refractory mania and aggressive behavior or psychotic symptoms.[40]

Acute Depression

Even though patients with bipolar disorder are depressed more of the time than they are manic or hypomanic, few studies have focused on the treatment of depression in this population, and only four drugs are currently approved by the FDA for the management of acute episodes of depression in patients with a bipolar disorder (Table 2). During a depressive episode, patients have a greater number of unacceptable side effects of pharmacologic treatments than they do during a manic episode. Therefore, a low initial dose with gradual upward dose adjustment is usually used.

Since only a limited number of drugs have been approved for the treatment of bipolar de-

Table 2. Drugs Approved by the Food and Drug Administration for the Management of Bipolar Disorder.

Drug	For Mania or Mixed Features	For Depression	Maintenance Therapy	Comments	Adverse Effects*
Mood stabilizers					
Lithium	Yes†	No	Yes	Antisuicidal effects	Hypothyroidism, increased calcium levels, reduced renal function
Carbamazepine, extended release	Yes	No	No		CYP450 induction, liver toxicity, agranulocytosis, rash, teratogenic effects
Divalproex					
Delayed release	Yes	No	No	Useful for the treatment of mixed states (i.e., concurrent manic and depressive symptoms)	CYP450 inhibition, teratogenic effects, liver toxicity, tremors, thrombocytopenia
Extended release	Yes	No	No	Useful for the treatment of mixed states (i.e., concurrent manic and depressive symptoms)	CYP450 inhibition, teratogenic effects, liver toxicity, tremors, thrombocytopenia
Lamotrigine	No	No	Yes	Useful for the prevention of depressive episodes; requires slow dose increase	Rash, Stevens–Johnson syndrome
Antipsychotic agents					
Aripiprazole	Yes†	No	Yes‡	Useful for mania-predominant polarity, favorable metabolic profile	Akathisia (restlessness and inability to sit still)
Arsenapine	Yes	No	No	May be efficacious for depressive symptoms	Akathisia, drowsiness, risk of metabolic syndrome
Cariprazine	Yes	Yes	No	Good metabolic profile	Akathisia
Chlorpromazine	Yes	No	No	Rapid effects	Risk of switch to depression, sedation, extrapyramidal symptoms
Lurasidone	No	Yes§	No	Should be ingested with food, favorable metabolic profile	Akathisia and sedation
Olanzapine	Yes	No	Yes	Rapid effects	Drowsiness, high risk of metabolic abnormalities
Olanzapine–fluoxetine	No	Yes	No		Drowsiness, high risk of metabolic abnormalities
Quetiapine					
Immediate release	Yes†§	Yes¶	Yes¶	Equally efficacious for prevention of manic and depressive episodes	Drowsiness, weight gain, metabolic abnormalities
Extended release	Yes	Yes¶	No	Equally efficacious for prevention of manic and depressive episodes	Drowsiness, weight gain, metabolic abnormalities
Risperidone	Yes	No	Yes	Available in a formulation for monthly intramuscular injection for maintenance therapy	Extrapyramidal side effects, weight gain, metabolic abnormalities, hyperprolactinemia
Ziprasidone	Yes	No	No‖	Useful for predominant manic polarity, good metabolic profile	Prolonged QTc interval on ECG, akathisia, hypotension

* CYP450 denotes cytochrome P-450, ECG electrocardiogram, and QTc corrected QT.
† This agent is approved for the treatment of juvenile bipolar disorder.
‡ This agent is available in formulations for oral or monthly intramuscular injection.
§ This agent is also approved as adjunctive therapy for patients receiving lithium or divalproex.
¶ This agent is also indicated for patients with bipolar II disorder.
‖ This agent is approved for maintenance therapy in combination with lithium or divalproex.

pression, other treatments, usually in combination, are often used off label in clinical practice. Some combination therapies, mainly antipsychotic agents and mood stabilizers, are supported by evidence from clinical trials. For example, the combination of olanzapine and fluoxetine was more efficacious than olanzapine alone in one meta-analysis.[46] Lithium combined with lamotrigine was superior to placebo plus lithium for bipolar depression (response rate, 51.6% vs. 31.7%).[47] Also, the combination of quetiapine and lamotrigine has been shown to be superior to quetiapine alone.[48] Lurasidone, which is approved by the FDA for the treatment of bipolar depression in adults, was effective in a 6-week, randomized, placebo-controlled trial for the management of acute episodes of bipolar depression in patients 10 to 17 years of age.[49] In a meta-analysis, the antipsychotic agent cariprazine was effective as monotherapy for the treatment of acute episodes of bipolar depression (Table 2).[50]

Small, randomized, controlled trials suggest the efficacy of pramipexole, ketamine, and scopolamine for the treatment of acute episodes of bipolar depression. Adjunctive treatment with antiinflammatory agents such as nonsteroidal antiinflammatory drugs, *N*-acetylcysteine, n–3 polyunsaturated fatty acids, and pioglitazone has been shown to have antidepressant effects in patients with bipolar depression.[51] However, weak trial design and implementation or small samples impeded conclusions regarding the efficacy and safety of these agents.

There is controversy regarding the efficacy and risks of antidepressant agents in managing bipolar depression. Treatment with antidepressants may carry a risk of switches to hypomania or mania during treatment ("affective switches") and acceleration of the cycling between them. Nevertheless, a meta-analysis has suggested that second-generation antidepressants (e.g., selective serotonin-reuptake inhibitors and bupropion) may be efficacious for the short-term management of bipolar depression[52]; effect sizes with antidepressants as compared with placebo were small, and there were no significant differences in response or remission rates. In view of these uncertainties, an expert panel concluded that evidence for the efficacy of antidepressants in the treatment of bipolar depression is limited but that individual patients may benefit from these drugs. Also, the risk of switches to mania appeared to be higher among patients with bipolar I disorder than among those with bipolar II disorder. Therefore, antidepressants are generally avoided in patients with type I bipolar disorder, but when necessary, they may be concomitantly prescribed with mood-stabilizing agents.[53] Treatments based on glutamatergic and γ-aminobutyric acid–related mechanisms are being tested for this indication.

ECT is effective for patients with treatment-resistant and multitherapy-resistant bipolar depression.[41] In addition, there is preliminary evidence for using adjuvant psychotherapeutic approaches in the management of bipolar depression, such as psychoeducation, cognitive behavioral therapy (CBT), family-focused therapy, dialectical behavioral therapy, and mindfulness-based CBT, as well as interpersonal and social rhythm therapy, which supports the incorporation of regular daily activities to restore circadian processes and improve mood[54]; however, effect sizes for these treatments have been small. For example, a meta-analysis showed that CBT mitigated depressive symptoms in patients with bipolar disorder, with small to moderate effect sizes.[55] In children and adolescents with bipolar depression, family education, in addition to skill building and CBT, has been effective, although larger controlled trials are needed to confirm this observation.[56] Finally, exercise may be beneficial for the management of acute bipolar depression; however, evidence for exercise as the sole approach is limited.[57]

MAINTENANCE TREATMENT

The chronic and recurring nature of bipolar disorder makes maintenance treatment important. Such treatment, aimed at preventing the emergence of affective episodes and burdensome affective symptoms, often requires a combination of pharmacologic, psychological, and lifestyle interventions. Ideally, maintenance treatment should be started shortly after the onset of illness.

Lithium remains one of the most effective drugs for the prevention of both depressive and manic recurrences in bipolar disorder. A network meta-analysis showed a risk ratio of 0.62 for relapse or recurrence with lithium as compared with a placebo.[58] The BALANCE trial was

a multicenter, randomized, open-label trial that assigned 330 participants with bipolar I disorder to lithium monotherapy, lithium plus valproate, or valproate monotherapy.[59] At 24 months, lithium monotherapy or lithium plus valproate was more efficacious than valproate monotherapy in preventing relapses.[59] These findings have been supported by a systematic review and meta-analysis, which showed that lithium is efficacious in the prevention of both manic and depressive episodes.[60] Despite the long-term effectiveness of lithium, side effects may emerge, including renal failure, hypothyroidism, polydipsia, polyuria, tremors, and an increase in peripheral calcium and parathyroid hormone levels.[61] Quetiapine alone and the combination of quetiapine–lithium or quetiapine–divalproex have also been shown in a trial to be effective maintenance treatments for bipolar disorder.[58] In another trial, no clinically meaningful differences were found when lithium treatment was compared with quetiapine, adjunctive quetiapine, and algorithm-based, personalized treatment.[62]

Many industry-sponsored trials of medications to treat bipolar disorder have used enriched designs, which make their results relevant to persons with an initial response to the drug in the trial and limit the generalizability of trial results. However, evidence showing the prophylactic effects of lithium come from randomized, controlled trials that did not have an enrichment design.[63] A meta-analysis showed that lithium, anticonvulsant agents, and antipsychotic agents may reduce long-term morbidity in juvenile bipolar disorder[64]; however, few trials were included in the analysis, and the results have been considered to be inconclusive.

All drugs used to treat bipolar disorder are associated with potential important side effects, and it is advisable to monitor patients throughout treatment. For example, serum thyrotropin, calcium, and lithium levels, as well as kidney function, are typically monitored in patients receiving lithium treatment. For patients treated with either divalproex or carbamazepine, liver enzyme levels are monitored regularly because of the risk of liver toxicity (Table 2). For patients receiving an atypical antipsychotic agent, weight and metabolic measures are monitored.

Divalproex and carbamazepine are teratogens and are therefore not recommended for women of childbearing age with bipolar disorder, particularly during the first trimester of pregnancy. The abrupt cessation of mood-stabilizing medications carries a high risk of relapse during pregnancy and in the postpartum period. Therefore, decisions regarding medication continuation are best made well in advance of a planned pregnancy.[65]

Maintenance ECT may be considered for patients with bipolar disorder who do not have a response to pharmacotherapy. Furthermore, adjunctive, evidence-based psychosocial treatments are efficacious and may prevent relapses and recurrences of major affective episodes during the maintenance phase of treatment.[66]

CONCLUSIONS

The diagnosis and treatment of bipolar disorder remain, to a large extent, subjective clinical exercises. Attention to the components of the disorder in an individual patient and to the response to each prescribed treatment is helpful in guiding therapy and providing a prognosis for the patient and family. Coexisting conditions, particularly medical disorders, are addressed as part of the overall treatment plan. Both pharmacologic and psychotherapeutic treatments have advantages and disadvantages and therefore require monitoring and skill in application. The development and validation of biomarkers for this disorder may allow earlier diagnosis and guide treatment selection, which are goals of precision psychiatry.[67]

Dr. Vieta reports receiving lecture fees from Abbott, Allergan, Lundbeck, and Sanofi, advisory board fees from Angelini and Sage, grant support, to be paid to his institution, from Sumitomo Dainippon Pharma and Ferrer, and grant support, paid to his institution, advisory board fees, and lecture fees from Janssen. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.com.

We thank Andre R. Brunoni, M.D., Ph.D., Mary Seeman, M.D., Roger S. McIntyre, M.D., and Abigail Ortiz, M.D., for important suggestions on earlier versions of the manuscript.

REFERENCES

1. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. Nat Rev Dis Primers 2018;4:18008.
2. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000;48:445-57.
3. Diagnostic and statistical manual of mental disorders, 5th ed.: DSM-5. Washington, DC: American Psychiatric Association, 2013.
4. Reed GM, First MB, Kogan CS, et al. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. World Psychiatry 2019;18:3-19.
5. Joslyn C, Hawes DJ, Hunt C, Mitchell PB. Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. Bipolar Disord 2016;18:389-403.
6. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry 2008;69:935-40.
7. Zimmerman M. Screening for bipolar disorder with self-administered questionnaires: a critique of the concept and a call to stop publishing studies of their performance in psychiatric samples. Depress Anxiety 2017;34:779-85.
8. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003;64:161-74.
9. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016;3:171-8.
10. Merikangas KR, Jin R, He J-P, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry 2011;68:241-51.
11. Zhang L, Cao X-L, Wang S-B, et al. The prevalence of bipolar disorder in China: a meta-analysis. J Affect Disord 2017;207:413-21.
12. Das AK, Olfson M, Gameroff MJ, et al. Screening for bipolar disorder in a primary care practice. JAMA 2005;293:956-63.
13. Daveney J, Panagioti M, Waheed W, Esmail A. Unrecognized bipolar disorder in patients with depression managed in primary care: a systematic review and meta-analysis. Gen Hosp Psychiatry 2019;58:71-6.
14. Bortolato B, Köhler CA, Evangelou E, et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Bipolar Disord 2017;19:84-96.
15. Miskowiak KW, Burdick KE, Martinez-Aran A, et al. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. Bipolar Disord 2018;20:184-94.
16. Plans L, Barrot C, Nieto E, et al. Association between completed suicide and bipolar disorder: a systematic review of the literature. J Affect Disord 2019;242:111-22.
17. Dong M, Lu L, Zhang L, et al. Prevalence of suicide attempts in bipolar disorder: a systematic review and meta-analysis of observational studies. Epidemiol Psychiatr Sci 2019;29:e63.
18. Carvalho AF, McIntyre RS, Dimelis D, et al. Predominant polarity as a course specifier for bipolar disorder: a systematic review. J Affect Disord 2014;163:56-64.
19. Krishnan KRR. Psychiatric and medical comorbidities of bipolar disorder. Psychosom Med 2005;67:1-8.
20. Brus MJ, Solanto MV, Goldberg JF. Adult ADHD vs. bipolar disorder in the DSM-5 era: a challenging differentiation for clinicians. J Psychiatr Pract 2014;20:428-37.
21. Maj M. "Psychiatric comorbidity": an artefact of current diagnostic systems? Br J Psychiatry 2005;186:182-4.
22. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am J Psychiatry 2013;170:265-74.
23. Fornaro M, Stubbs B. A meta-analysis investigating the prevalence and moderators of migraines among people with bipolar disorder. J Affect Disord 2015;178:88-97.
24. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 2016;15:166-74.
25. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72:334-41.
26. Hayes JF, Miles J, Walters K, King M, Osborn DPJ. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand 2015;131:417-25.
27. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. J Affect Disord 2015;180:142-7.
28. Firth J, Siddiqi N, Koyanagi A, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry 2019;6:675-712.
29. Gordovez FJA, McMahon FJ. The genetics of bipolar disorder. Mol Psychiatry 2020;25:544-59.
30. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 2019;51:793-803.
31. Misiak B, Stramecki F, Gawęda Ł, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. Mol Neurobiol 2018;55:5075-100.
32. Post RM. Epigenetic basis of sensitization to stress, affective episodes, and stimulants: implications for illness progression and prevention. Bipolar Disord 2016;18:315-24.
33. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011;35:804-17.
34. Hibar DP, Westlye LT, Doan NT, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry 2018;23:932-42.
35. Belvederi Murri M, Prestia D, Mondelli V, et al. The HPA axis in bipolar disorder: systematic review and meta-analysis. Psychoneuroendocrinology 2016;63:327-42.
36. Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry 2017;16:236-44.
37. Morris G, Puri BK, Walker AJ, et al. Shared pathways for neuroprogression and somatoprogression in neuropsychiatric disorders. Neurosci Biobehav Rev 2019;107:862-82.
38. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 2016;134:91-103.
39. Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: system-

atic review and meta-analysis. Am J Psychiatry 2012;169:790-804.
40. Fountoulakis KN, Yatham LN, Grunze H, et al. The CINP guidelines on the definition and evidence-based interventions for treatment-resistant bipolar disorder. Int J Neuropsychopharmacol 2020;23:230-56.
41. Hidalgo-Mazzei D, Berk M, Cipriani A, et al. Treatment-resistant and multitherapy-resistant criteria for bipolar depression: consensus definition. Br J Psychiatry 2019;214:27-35.
42. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med 2015;45:299-317.
43. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011; 378:1306-15.
44. Grande I, Vieta E. Pharmacotherapy of acute mania: monotherapy or combination therapy with mood stabilizers and antipsychotics? CNS Drugs 2015;29:221-7.
45. Geller B, Luby JL, Joshi P, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry 2012;69:515-28.
46. Silva MT, Zimmermann IR, Galvao TF, Pereira MG. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. J Affect Disord 2013;146:310-8.
47. van der Loos MLM, Mulder PGH, Hartong EGTM, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:223-31.
48. Geddes JR, Gardiner A, Rendell J, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 × 2 factorial randomised trial. Lancet Psychiatry 2016;3:31-9.
49. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry 2017; 56:1015-25.
50. Pinto JV, Saraf G, Vigo D, Keramatian K, Chakrabarty T, Yatham LN. Cariprazine in the treatment of bipolar disorder: a systematic review and meta-analysis. Bipolar Disord 2019 October 16 (Epub ahead of print).
51. Rosenblat JD, Kakar R, Berk M, et al. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disord 2016;18:89-101.
52. McGirr A, Vöhringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry 2016; 3:1138-46.
53. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013;170:1249-62.
54. Chatterton ML, Stockings E, Berk M, Barendregt JJ, Carter R, Mihalopoulos C. Psychosocial therapies for the adjunctive treatment of bipolar disorder in adults: network meta-analysis. Br J Psychiatry 2017;210:333-41.
55. Chiang K-J, Tsai J-C, Liu D, Lin C-H, Chiu H-L, Chou K-R. Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: a meta-analysis of randomized controlled trials. PLoS One 2017; 12(5):e0176849.
56. Fristad MA. Evidence-based psychotherapies and nutritional interventions for children with bipolar spectrum disorders and their families. J Clin Psychiatry 2016;77:Suppl E1:e4.
57. Melo MCA, Daher EDF, Albuquerque SGC, de Bruin VMS. Exercise in bipolar patients: a systematic review. J Affect Disord 2016;198:32-8.
58. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:351-9.
59. Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010; 375:385-95.
60. Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord 2014;2:15.
61. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet 2012;379: 721-8.
62. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. J Clin Psychiatry 2016;77: 90-9.
63. Licht RW. Lithium: still a major option in the management of bipolar disorder. CNS Neurosci Ther 2012;18:219-26.
64. Yee CS, Hawken ER, Baldessarini RJ, Vázquez GH. Maintenance pharmacological treatment of juvenile bipolar disorder: review and meta-analyses. Int J Neuropsychopharmacol 2019;22:531-40.
65. Anmella G, Pacchiarotti I, Cubala WJ, et al. Expert advice on the management of valproate in women with bipolar disorder at childbearing age. Eur Neuropsychopharmacol 2019;29:1199-212.
66. Salcedo S, Gold AK, Sheikh S, et al. Empirically supported psychosocial interventions for bipolar disorder: current state of the research. J Affect Disord 2016; 201:203-14.
67. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry.' BMC Med 2017;15:80.