Bipolar disorders

Roger S McIntyre, Michael Berk, Elisa Brietzke, Benjamin I Goldstein, Carlos López-Jaramillo, Lars Vedel Kessing, Gin S Malhi, Andrew A Nierenberg, Joshua D Rosenblat, Amna Majeed, Eduard Vieta, Maj Vinberg, Allan H Young, Rodrigo B Mansur

Bipolar disorders are a complex group of severe and chronic disorders that includes bipolar I disorder, defined by the presence of a syndromal, manic episode, and bipolar II disorder, defined by the presence of a syndromal, hypomanic episode and a major depressive episode. Bipolar disorders substantially reduce psychosocial functioning and are associated with a loss of approximately 10–20 potential years of life. The mortality gap between populations with bipolar disorders and the general population is principally a result of excess deaths from cardiovascular disease and suicide. Bipolar disorder has a high heritability (approximately 70%). Bipolar disorders share genetic risk alleles with other mental and medical disorders. Bipolar I has a closer genetic association with schizophrenia relative to bipolar II, which has a closer genetic association with major depressive disorder. Although the pathogenesis of bipolar disorders is unknown, implicated processes include disturbances in neuronal-glial plasticity, monoaminergic signalling, inflammatory homoeostasis, cellular metabolic pathways, and mitochondrial function. The high prevalence of childhood maltreatment in people with bipolar disorders and the association between childhood maltreatment and a more complex presentation of bipolar disorder (eg, one including suicidality) highlight the role of adverse environmental exposures on the presentation of bipolar disorders. Although mania defines bipolar I disorder, depressive episodes and symptoms dominate the longitudinal course of, and disproportionately account for morbidity and mortality in, bipolar disorders. Lithium is the gold standard mood-stabilising agent for the treatment of people with bipolar disorders, and has antimanic, antidepressant, and anti-suicide effects. Although antipsychotics are effective in treating mania, few antipsychotics have proven to be effective in bipolar depression. Divalproex and carbamazepine are effective in the treatment of acute mania and lamotrigine is effective at treating and preventing bipolar depression. Antidepressants are widely prescribed for bipolar disorders despite a paucity of compelling evidence for their short-term or long-term efficacy. Moreover, antidepressant prescription in bipolar disorder is associated, in many cases, with mood destabilisation, especially during maintenance treatment. Unfortunately, effective pharmacological treatments for bipolar disorders are not universally available, particularly in low-income and middle-income countries. Targeting medical and psychiatric comorbidity, integrating adjunctive psychosocial treatments, and involving caregivers have been shown to improve health outcomes for people with bipolar disorders. The aim of this Seminar, which is intended mainly for primary care physicians, is to provide an overview of diagnostic, pathogenetic, and treatment considerations in bipolar disorders. Towards the foregoing aim, we review and synthesise evidence on the epidemiology, mechanisms, screening, and treatment of bipolar disorders.

Lancet 2020; 396: 1841–56

Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada (Prof R S McIntyre FRCPsych, J D Rosenblat FRCPsych, A Majeed FRCPsych, R B Mansur FRCPsych); **Department of Psychiatry** (Prof R S McIntyre, J D Rosenblat, R B Mansur, A A Nierenberg FRCPsych, Prof B I Goldstein FRCPsych) **and Department of Pharmacology** (Prof R S McIntyre), **University of Toronto, Toronto, ON, Canada; Brain and Cognition Discovery Foundation, Toronto, ON, Canada** (Prof R S McIntyre); **Institute for Mental and Physical Health and Clinical Translation Strategic Research Centre, School of Medicine, Deakin University, Melbourne, VIC, Australia** (Prof M Berk FRCPsych); **Mental Health Drug and Alcohol Services, Barwon Health, Geelong, VIC, Australia** (Prof M Berk); **Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, VIC, Australia** (Prof M Berk); **Centre for Youth Mental Health, Florey Institute for Neuroscience and Mental Health, Melbourne, VIC, Australia** (Prof M Berk); **Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia** (Prof M Berk); **Department of Psychiatry, Adult Division, Kingston General Hospital, Kingston, ON, Canada** (Prof E Brietzke FRCPsych); **Department of Psychiatry, Queen's University School of Medicine,** (Prof E Brietzke) **and Centre for Neuroscience Studies** (Prof E Brietzke), **Queen's University, Kingston, ON, Canada; Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (Prof B I Goldstein); **Department of Psychiatry, Faculty of Medicine, University of Antioquia, Medellín, Colombia** (Prof C López-Jaramillo FRCPsyc); **Mood Disorders Program,**

Introduction

Bipolar disorders are a group of chronic mental disorders that include bipolar I disorder and bipolar II disorder (panel 1). Bipolar I disorder is defined by the presence of a syndromal, manic episode, and has an estimated global lifetime prevalence of 0·6–1·0%.[1] Bipolar II disorder is defined by the presence of a syndromal, hypomanic episode and a major depressive episode, and has an estimated global lifetime prevalence of 0·4–1·1%.[1] The foregoing estimates have largely been derived from studies of high-income countries; in low-income and middle-income countries, the lifetime prevalence of bipolar disorders has been variably reported. For example, the lifetime prevalence of bipolar disorders is approximately 0·1–1·8% in Ethiopia and Nigeria, and 3·0–4·0% in South Africa.[2,3] Although some individuals with bipolar I disorder might experience only manic or predominantly manic episodes, most people with bipolar I disorder are differentially affected by depressive symptoms and episodes.[4] A highly replicated finding in studies of people with bipolar disorders is the early age of onset, wherein more than 70% of individuals with bipolar disorders manifest clinical characteristics of the illness before the age of 25 years.[5,6]

The association of bipolar disorders with creativity, professional accomplishment, and political and organisational leadership is amply documented.[7] Notwithstanding the accomplishments and function of many people with bipolar disorders, most affected individuals have

Key messages

- Bipolar disorders are associated with premature mortality, with deaths from cardiovascular disease being the most common cause
- Although the pathogenesis of bipolar disorders is unknown, approximately 70% of the risk for bipolar disorders is heritable
- Multidisciplinary primary care physicians should screen patients who present with depressive symptoms for current and past history of hypomania or mania at initial consultation and at subsequent visits if an insufficient response to treatment is observed
- Lithium is the gold standard mood-stabilising agent in bipolar disorders, is capable of reducing suicidality, and should be prioritised in treatment sequencing for both mania and depression

Hospital Universitario San Vicente Fundación, Medellín, Colombia (Prof C López-Jaramillo); **Copenhagen Affective Disorders Research Centre, Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark** (Prof L Vedel Kessing FRCPsych); **Department of Psychiatry, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (Prof L Vedel Kessing, Prof M Vinberg FRCPsych); **Psychiatric Research Unit, Psychiatric Centre North Zealand, Hillerød, Denmark** (Prof M Vinberg); **Discipline of Psychiatry, Northern Clinical School, University of Sydney, Sydney, NSW, Australia** (Prof G S Malhi FRCPsych); **Department of Academic Psychiatry, Northern Sydney Local Health District, Sydney, Australia** (Prof G S Malhi); **Dauten Family Center for Bipolar Treatment Innovation, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA** (J D Rosenblat); **Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain** (Prof E Vieta FRCPsych); **and Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London and South London and Maudsley National Health Service Foundation Trust, Bethlem Royal Hospital, London, UK** (Prof A H Young FRCPsych)

Correspondence to:
Prof Roger S McIntyre, Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON M5T 2S8, Canada
roger.mcintyre@uhn.ca

Search strategy and selection criteria

We searched PubMed for review articles, clinical studies, and meta-analyses published in the English language between Jan 1, 2010, and March 1, 2020, using the term "bipolar disorder" cross-referenced with "screening", "diagnostic criteria", "comorbidity", "depression", "mixed features", "guidelines", "management", "clinical treatment", "economics", and "cost". The emphasis was on articles published during the past decade. Moreover, to decrease the number of citations and to increase the probability of identifying articles relevant to this Seminar, priority was given to those papers that used meta-analytic methodology. To help to mitigate bias inherent to this non-systematic review, RSM brought together individuals from Australia, Brazil, Canada, Europe, and the USA who not only have made original contributions to bipolar disorder literature, but are also experienced clinicians in the field. The international perspective was intended to capture diverse views, help to balance the discussion, and ensure adequate representation of key areas of development in the field. RSM prepared the initial draft of the manuscript after receiving feedback from authors regarding priority topics in bipolar disorder.

substantial illness-related disability, reduced psychosocial functioning, and increased economic costs.[8] Actuarial cost estimates of bipolar disorders in the USA are more than US$202 billion.[8] Evidence also indicates that a substantial percentage of the cost of bipolar disorders is due to comorbid, chronic non-communicable diseases that disproportionately affect people with bipolar disorders (eg, cardiovascular disease).[9] Although few cost-of-illness studies for bipolar disorders have been done in low-income and middle-income countries, health-care expenditures for all mental disorders in these countries are disconcertingly low. Only $0·10 per capita is spent on mental health services by governments in African countries compared with an average of $21·70 spent among European nations.[3,10]

Mortality studies indicate that bipolar disorders, similar to schizophrenia, are associated with a loss of approximately 10–20 potential years of life.[11–13] The mortality gap between individuals with bipolar disorders and the general population is vast and increasing, especially in younger populations (aged 15–29 years).[14–16] Cardiovascular disease is the most common cause of premature mortality in people with bipolar disorders. Results from Denmark indicate that, at age 15 years, the remaining life expectancy for a person with bipolar disorder is 9–13 years less than that of the general population.[17,18] The high prevalence of medical comorbidity in bipolar disorders underscores the need for an integrated approach to the assessment and management of individuals with this group of mental disorders.

Moreover, people with bipolar disorders die by suicide more frequently than do people with all other mental disorders.[19,20] People with bipolar disorders are approximately 20–30 times more likely to die by suicide compared with the general population. Indeed, approximately 30–50% of adults with bipolar disorders have a lifetime history of suicide attempts, with an estimated 15–20% of affected people dying by suicide.[19] Suicide attempts and dying by suicide are more likely to occur in people who have depressive or mixed symptoms as part of their bipolar disorder than in those who do not. Available evidence also suggests that bipolar II disorder has a higher suicide rate than does bipolar I disorder, underscoring the complexity and severity of bipolar II.[21]

The foregoing portrait of bipolar disorders as a highly prevalent and chronic group of disorders associated with substantial morbidity and mortality provided the impetus for this Seminar. The aim of this Seminar, intended mainly for multidisciplinary primary care physicians, is to provide an overview of diagnostic, pathogenetic, and treatment considerations in bipolar disorders. Towards the foregoing aim, we review and synthesise evidence on the epidemiology, mechanisms, screening, and treatment of bipolar disorders.

Diagnostic criteria and differential diagnosis

The diagnosis of bipolar disorders is made by a comprehensive clinical assessment, and supplemented, when possible, with third-party information (eg, from family members). Unfortunately, there is no biomarker (eg, genetic test) that informs the diagnosis, prognosis, or treatment outcome of bipolar disorders. Often, arriving at a probable working diagnosis of bipolar disorder during an initial consultation is impossible, inviting the need for longitudinal assessment supplemented with mood diaries and corroborative information. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) and the *International Classification of Diseases*, 10th revision (ICD-10) operationalise the definition of bipolar disorders (panel 1).[22]

The DSM-5 has amended the diagnostic criteria of the text revised fourth edition of the DSM (known as the DSM-IV-TR) for mania and hypomania to include persistently increased energy or activity along with elevated, expansive, or irritable mood as essential features. Hence, diagnosing mania on mood instability alone is no longer sufficient; instead, the co-occurrence of mood instability with increased energy or activity is required. Another important change in the DSM-5 (but not in the ICD-10 or the 11th revision of the ICD) was supplanting mixed states (ie, syndromal mania and depression) with the mixed features specifier (panel 2). The DSM-5 defined the mixed features specifier as the presence of opposite polarity symptoms during a manic or major depressive episode. Although some symptoms of mania and depression overlap (eg, agitation), the DSM-5 does not include these overlapping symptoms in the diagnostic criteria for mixed features. Taken together, clinicians

should be aware that individuals with bipolar disorders presenting with depression will often manifest symptoms of anxiety, agitation, anger-irritability, and attentional disturbance-distractibility (the four As), all of which are highly suggestive of mixed features. The clinical relevance of detecting mixed features is that antidepressant medication should not be prescribed to adults with bipolar disorders presenting with mixed features.[23–31]

The differential diagnosis of bipolar disorders includes other mental disorders characterised by impulsivity, affective instability, anxiety, cognitive disorganisation, depression, and psychosis. For example, although depression is the predominant and index presentation of bipolar disorder, differentiating bipolar disorder from major depressive disorder is the most common clinical challenge for most clinicians. Features that would suggest a greater probability that a patient who presents with depression has bipolar disorder, rather than major depressive disorder, are an earlier age at onset of illness, phenomenology (eg, hyperphagia, hypersomnia, and psychosis are more common in bipolar disorders than in major depressive disorder), a higher frequency of affective episodes, pattern of comorbidity (eg, substance use disorders, anxiety disorders, binge eating disorders, and migraines all disproportionately affect people with bipolar disorders), and family history of psychopathology.[32] Also potentially informing the diagnosis of bipolar disorders is an insufficient response to antidepressants, which is known to occur more often in adults with bipolar disorders than in those with major depressive disorder. Furthermore, amplification of anxiety, dysphoria, and mood instability in a person administered antidepressants should increase suspicion of underlying bipolar disorders.[32]

Other differential diagnoses to consider in people with possible bipolar disorders are attention-deficit hyperactivity disorder (ADHD), borderline personality disorder, substance use disorders, and schizophrenia. The guiding principle when differentiating bipolar disorders from each of the foregoing mental disorders is similar to that described when differentiating from major depressive disorder (ie, external validators [eg, age at onset, course of illness, and family history]).

The differentiation of bipolar disorders from ADHD is informed by an earlier age of onset of symptoms in ADHD than in bipolar disorders and the absence of psychosis and affective episodes in people with ADHD. Differentiating bipolar disorders from borderline personality disorder is informed by the core disturbance in attachment that is central to the definition of borderline personality disorder but is not a defining feature of bipolar disorders. In contradistinction, syndromal affective episodes and associated disturbances in circadian rhythm are more suggestive of bipolar disorder than of borderline personality disorder. Moreover, people with borderline personality disorder are more likely to exhibit rapid shifts in mood states associated with interpersonal dysfunction than are people with bipolar disorders. Additionally, unlike bipolar disorder, the psychopathology of borderline personality disorder often attenuates with age.

Approximately 50–60% of adults with bipolar disorders have a current, or lifetime, comorbid alcohol use disorder, a substance use disorder, or both.[33] Differentiation of bipolar disorders from alcohol use disorders and substance use disorders is done through patient observation during periods of sobriety (where possible). Clinicians are encouraged to be vigilant of the association between consumption of psychoactive substances and the presence of psychopathology.[32] The presence of

***Panel 1*: Diagnostic criteria for bipolar disorders and related disorders**

DSM-5 diagnostic criteria

Bipolar I disorder

Criteria met for at least one manic episode, which might have been preceded or followed by a hypomanic episode or major depressive disorder; a depressive episode or psychosis do not have to be present for a diagnosis.

Bipolar II disorder

Criteria met for at least one current or past hypomanic episode and a major depressive episode; no manic episodes.

Cyclothymic disorder

Hypomanic symptoms that do not meet the criteria for hypomanic episodes and depressive symptoms that do not meet the criteria for major depressive episodes in numerous periods (at least half the time) for at least 2 years (1 year in those aged ≤18 years); criteria for major depressive, manic, or hypomanic episodes have never been met.

Other specified bipolar disorder

Bipolar-like phenomena that do not satisfy the criteria for bipolar I disorder, bipolar II disorder, or cyclothymic disorder (ie, short-duration hypomanic episodes and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, a hypomanic episode without a previous major depressive episode, and short-duration cyclothymia).

Unspecified bipolar and related disorder

Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, but do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class.

ICD-10 diagnostic criteria

Bipolar disorder

Characterised by two or more episodes in which the patient's mood and activity levels are considerably disturbed (ie, elevation of mood and increased energy and activity [hypomania or mania] or lowering of mood and decreased energy and activity [depression]). Repeated episodes of hypomania or mania only are classified as bipolar. To harmonise with DSM-5, ICD-11 distinguishes between bipolar I disorder and bipolar II disorder despite mixed evidence of a distinct separation.

Cyclothymic disorder

Persistent instability of mood involving numerous periods of depression and mild elation that are not sufficiently severe or prolonged to satisfy a diagnosis of bipolar affective disorder or recurrent depressive disorder.

DSM-5=*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition. ICD-10=*International Classification of Diseases*, 10th revision. ICD-11=*International Classification of Diseases*, 11th revision.

Panel 2: Distinction between mixed episode and mixed features specifier

Mixed episode

- Described in the DSM-IV-TR
- Requires an individual to simultaneously meet the criteria for a major depressive episode and a manic episode

Mixed features specifier

- Described in the DSM-5
- Can be applied to episodes of major depression, mania, and hypomania
- Requires the presence of at least three manic or hypomanic non-overlapping symptoms during a major depressive episode
- Requires the presence of at least three depressive non-overlapping symptoms during a hypomanic or manic episode

DSM-IV-TR=*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revised. DSM-5=*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition

Panel 3: Factors increasing the probability of a diagnostic change from major depressive disorder to bipolar disorders

- Earlier age at onset (ie, <25 years)
- Presence of psychosis
- Atypical depression (eg, hyperphagia or hypersomnia)
- Number of depressive episodes (ie, three or more previous episodes)
- A family history of bipolar disorders, an extensive family loading of psychopathology, or both
- Non-response to antidepressants or the induction of hypomanic symptoms by antidepressant treatment
- Mixed features
- Pattern of comorbidity (eg, substance use disorder and migraine) and polymorbidity (three or more comorbid conditions)

phenomenology related to bipolar disorders before the onset of alcohol use disorders or substance use disorders, or bipolar phenomenology that persists during periods of sobriety, would be more likely to suggest an underlying diagnosis of bipolar disorder. Clinicians are reminded, however, that the diagnoses of ADHD, borderline personality disorder, alcohol use disorders, and substance use disorders are potentially comorbid and additional rather than diagnoses of exclusion.[32,34–36]

Differentiating bipolar disorders from schizophrenia is often difficult at the first episode of illness because both conditions often present with prominent psychosis and mood symptoms. Longitudinally, however, people with schizophrenia exhibit psychosis as the primary clinical presentation in the absence of clinically significant mood symptoms, and are also more likely to show greater psychosocial impairments and less favourable illness trajectories than are those with bipolar disorders. In contradistinction, people with bipolar disorders exhibit affective episodes and symptoms as the predominant illness presentation and, in general, do not exhibit the extent of psychosocial impairment that is often seen in people with schizophrenia.

Screening and diagnosing bipolar disorders

An accurate and timely diagnosis of bipolar disorders is an unmet need in this population. Most individuals with bipolar disorders are not accurately diagnosed until approximately 6–10 years after first contact with a primary health-care provider, a specialty health-care provider, or both, despite having clinical characteristics of the illness.[37]

Misdiagnosing bipolar disorders, however, is separate from the often encountered clinical scenario wherein a patient's diagnosis transitions from major depressive disorder to bipolar disorder. For example, most people with bipolar disorders have depressive episodes as the index presentation, with hypomania and mania presenting later. Angst and colleagues[38] reported a rate of diagnostic change from major depressive disorder to bipolar disorder of 1·25% per year, but separate reports have estimated change rates of up to 20–30% within 3 years.[39] Practitioners should remain vigilant for bipolar disorders in any person who initially screens negative for bipolar disorders, but presents at a later time with clinically significant affective symptoms (panel 3).[37,39–42]

The high rates of missed diagnosis of bipolar disorders and longitudinal transition from major depressive disorder to bipolar disorders provide the impetus for routine and systematic screening for bipolar disorders in all patients presenting with depressive symptomatology. Several self-report screening tools for bipolar disorders have been validated and made available at no cost in multiple languages.[43] The most studied screening tools for bipolar disorders are the Mood Disorders Questionnaire and the Hypomania Checklist 32.[44] For the Mood Disorders Questionnaire, the reported sensitivity is 80% (95% CI 71–86) and the reported specificity is 70% (59–71).[44] For the Hypomania Checklist 32, the reported sensitivity is 82% (95% CI 72–89) and the reported specificity is 57% (48–66). These screening tools are intended for use at point of care and, if positive, invite the need for a careful and thorough clinical assessment for bipolar disorders.

Comorbidity in bipolar disorders

The lifetime prevalence of psychiatric and medical comorbidities in adults with bipolar disorders is estimated to be approximately 90%.[45] Additionally, approximately 50% of individuals with bipolar disorders are affected by polymorbidity (ie, have three or more comorbid conditions).[46,47] Comorbidity in bipolar disorders is associated with an earlier age at onset and a more complex presentation of bipolar disorders, higher rates of suicidality, and a less favourable treatment response and

prognosis than are bipolar disorders without comorbidity. The observation that adults with bipolar disorders and multiple previous affective episodes have higher rates of comorbidity compared with individuals with first-episode mania provides an opportunity for primary and secondary prevention. For example, in people who are newly diagnosed with bipolar disorders, education and counselling for the risk of alcohol use disorders and substance use disorders should be provided regardless of whether the individual is currently misusing substances. The high rates of comorbidities in people with multi-episode bipolar disorders is likely due, in part, to the effects of age (eg, cardiovascular disease), but might also be explained by neurophysiological changes that accompany each episode (eg, changes in brain volume).[48,49]

Anxiety disorders are the most commonly encountered psychiatric comorbidity in people with bipolar disorders; approximately 70–90% of people with bipolar disorders meet the criteria for either generalised anxiety disorder, social anxiety disorder, or panic disorder.[50] About 30–50% of adults with bipolar disorders have either substance use disorder or alcohol use disorder and 25–45% meet the criteria for ADHD.[33,51] Personality disorders (20–40%) and binge eating disorder (10–20%) are also recognised as being common in people with bipolar disorders.[52] Taken together, the high prevalence of, and hazards posed by, psychiatric comorbidity in people with bipolar disorders invites the need for screening people with bipolar disorders for concurrent psychiatric conditions.[33,50–52]

The high prevalence of psychiatric comorbidity in bipolar disorders might, in some cases, reflect overlapping pathogenesis. For instance, brain regions implicated in affective instability and cognitive function in bipolar disorders are also implicated in ADHD and anxiety disorders. In some cases, what appears to be comorbidity in childhood, manifesting as ADHD, anxiety disorders, or both, might in fact be a phenotypic variant of bipolar disorders rather than a discrete comorbid condition (ie, heterotypic continuity).[47,53] The higher prevalence of alcohol and drug misuse in people with multi-episode bipolar disorder compared with first-episode bipolar disorder is suggestive of progressive disturbance in cognitive control, in reward-based decision making, or in both, which predisposes to the comorbidity of drug and alcohol misuse.

Further evidence for the shared pathogenesis between bipolar disorders and comorbidity is the high prevalence of cardiovascular disorders at index presentation in individuals with bipolar disorders.[54] Bipolar disorder is a risk factor for cardiovascular disease, reflecting intrinsic and shared causal substrates.[55–57] The staggering rates of cardiovascular disease and related risk factors (eg, obesity) and their contribution to premature mortality in people with bipolar disorders are a rationale for prioritising both the physical and mental health of patients with bipolar disorders.

Causes and pathogenesis of bipolar disorders

Twin studies report that the heritability of bipolar disorders is approximately 60–80%.[58,59] The concordance of bipolar disorders is approximately 40–45% for monozygotic twins and 4–6% for dizygotic twins.[60] Bipolar I disorder is highly genetically correlated with schizophrenia and bipolar II disorder is highly genetically correlated with major depressive disorder.[61] Genome-wide association studies have identified approximately 30 common genetic variants with significant associations with bipolar disorders, each with small effect sizes.[61,62] Susceptibility loci for bipolar disorders provide indirect insights into the pathogenesis of bipolar disorders.

Two separate genome-wide association studies[61,62] have identified loci significantly associated with bipolar disorders that contain genes encoding ion channels (eg, *CACNA1C* and *SCN2A*), proteins involved in signal transduction (eg, *DGKH*), neurotransmitter transporters (eg, *GRIN2A*), and synaptic plasticity proteins (eg, *ANK3*). Gene sets regulating insulin secretion and endocannabinoid signalling have also been implicated in bipolar disorders.[61] The genetic architecture of bipolar disorders has been reported to overlap with other neurological and psychiatric disorders (eg, migraine, autism spectrum disorder, and anxiety) and intelligence.[63] Notwithstanding their genetic basis, genetic testing to diagnose bipolar disorders is not currently validated or recommended and, instead, diagnosis remains a clinical endeavour.[61]

An exciting new technology that might provide insight into the pathogenesis of bipolar disorders, and the mechanism of action of treatments for bipolar disorders, is human induced pluripotent stem cells.[64] Pluripotent stem cells are derived from somatic cells that are easily accessible (eg, buccal mucosa). Preliminary evidence gained by use of this technology suggests that mitochondrial dysfunction might be relevant to the pathogenesis of bipolar disorders. These observations with human induced pluripotent stem cells accord with results from studies that use magnetic resonance spectroscopy, which have also implicated disturbances in mitochondrial function in bipolar disorders.[65–67] Notwithstanding the promise of human induced pluripotent stem cells, this technology is highly investigational and the role these methods have in informing disease modelling and new therapeutics is unknown.

Replicated evidence suggests that inflammatory disturbance might contribute to the pathogenesis of bipolar disorders.[68,69] For example, alterations in both central and peripheral immune proteins (eg, C-reactive protein, IL-1, and IL-6) have been reported in people with bipolar disorders.[69] The activated inflammatory system in bipolar disorder is, in part, related to lifestyle and environmental exposures that are more common in people with bipolar disorders than in those without bipolar disorders (eg, smoking, poor diet, physical inactivity, and trauma).[70,71] Infectious activation of the

inflammatory system in bipolar disorders is suggested by evidence of high seropositivity to select infectious agents and exposure to infectious agents in utero (eg, *Toxoplasma gondii*, cytomegalovirus, and herpes simplex virus).[72–74] Despite the accumulating evidence implicating inflammatory systems in the pathogenesis of bipolar disorders, the precise role of these systems in bipolar disorders is still not fully understood.[75] Similarly, several lines of evidence suggest that disturbances in central insulin signalling and function might also be part of the pathogenesis of bipolar disorders in some cases. For instance, people with bipolar disorders have a higher prevalence of type 2 diabetes and a higher risk of Alzheimer's disease than do people without bipolar disorders.[76–79] However, interpreting this observation with respect to insulin disturbances in people with bipolar disorders is complicated by other potential confounding factors, notably the exposure to psychotropic agents that promote weight gain and the tendency for people with bipolar disorders to have unhealthy lifestyles.[80–83]

The neurobiological progression hypothesis is the notion that people with bipolar disorders might exhibit progressive neurobiological changes as a function of illness duration and the number of previous episodes. Neurobiological progression in bipolar disorders is suggested by longitudinal phenomenological, neurostructural, cognitive, neurochemical, and biochemical data.[84,85] Moreover, waning treatment response to pharmacological agents, cognitive behavioural therapy, and psychoeducation in people with multi-episode bipolar disorders with time indirectly supports the neurobiological progression hypothesis.[86–88] However, the generalisation of these data is limited by the fact that many patients included in these studies have a history of multiple hospitalisations and so the findings might not apply to adults with bipolar disorders but no history of hospitalisation. Available evidence suggests that early initiation of lithium (ie, after an index episode of mania) can, in some cases, alter the neurobiological progression of bipolar disorders.[89,90] The notion of neuroprogression in bipolar disorders provides the basis for the use of staging models akin to other medical disorders.[85,91]

A coherent and comprehensive pathogenetic model of bipolar disorders must also integrate the impact of trauma on the risk and course of bipolar. One study[92] found that 50 (50%) of 100 patients with bipolar disorders reported a history of adverse childhood experiences. History of childhood maltreatment in adults with bipolar disorders is associated with an earlier age at onset of illness. Higher rates of trauma reported in samples of people with bipolar disorders from the USA compared with samples of people with bipolar disorders from Germany and the Netherlands could account for the earlier age of onset of bipolar disorders in the USA than in Germany or the Netherlands.[93] Compared with having no history, a history of childhood maltreatment is associated with more severe depressive symptoms, higher rates of suicidality, a more complex presentation of illness (eg, rapid cycling and suicidality), higher rates of comorbidities (eg, anxiety, obesity, and substance use disorders), and decreased response to treatment in bipolar disorders.[94–97]

Management strategies for bipolar disorders

The therapeutic objectives in bipolar disorders are: the prevention and treatment of syndromal hypomania, mania, and depression; the abatement of interepisodic depressive symptoms; the normalisation of circadian disturbances (eg, in sleep); the improvement and preservation of cognitive function; the treatment and prevention of psychiatric and medical comorbidity; the improvement of patient-reported outcomes (eg, quality of life); and the reduction of suicidality.

The suboptimal effectiveness of treatments for bipolar disorders is underscored by evidence indicating that the relapse rate for individuals who recover from first-episode mania is approximately 40–60% within 1–2 years.[98–100] One study reported that only 65 (37%) of 176 adults discharged from hospital after first-episode mania had full syndromal and functional recovery 18 months later.[101] Generally, recovery rates are higher for individuals with fewer episodes and shorter illness durations, underscoring the need for timely diagnosis and initiation of effective treatment. Moreover, individuals with classic bipolar presentations (eg, elated mania), stable episodic courses of illness, an absence of rapid cycling and comorbidity, psychosocial support, and who are receiving care through specialised treatment programmes have better illness outcomes than do those without these features and support systems.[102]

One study has reported that an implementation gap exists with respect to point-of-care, evidence-based best practices for people with bipolar disorders.[103] In addition to narrowing implementation gaps and incorporating guideline-concordant, measurement-based care, integrating specialty services into the continuum of care has been shown to improve health outcomes in people with bipolar disorders.[102,104–106] In particular, greater attention to physical health in adults with bipolar disorders needs to be prioritised given the high rates of chronic medical disorders, habitual inactivity, poor food choices, current smoking (ie, approximately 40–60% of patients with bipolar disorders smoke tobacco), and weight gain, and concerns over the tolerability of medications for bipolar, in populations of people with bipolar disorders.[107–109]

Treatment discovery and development for bipolar disorders has largely been done in high-income countries and in samples with low racial, ethnic, and economic diversity. Moreover, pharmacological treatments for bipolar disorders have been largely developed for the purpose of regulatory approval, with less emphasis on patient-reported outcomes (eg, quality of life, wellbeing, and function). In addition, not all treatments that have been established as efficacious in bipolar disorders are

available in all countries, resulting in disparate treatment practices and health outcomes.

The guiding principles in the management of bipolar disorders are to incorporate measurement-based care, prioritise treatments that have the most compelling evidence base, consider short-term and long-term safety and tolerability (eg, weight gain), integrate guideline-informed treatment decisions, prioritise both mental and physical wellbeing, and involve patients and stakeholders in the treatment decision making process. High rates of interpersonal dysfunction, relationship discord, vocational loss and maladjustment, comorbidity, human suffering, trauma, and suicidality warrant, in many cases, adjunctive manual-based therapies (eg, cognitive behavioural therapy). Insufficient diagnostic and treatment literacy, stigma, misinformation, and cultural differences with respect to attitudes towards bipolar disorders and their treatment warrant psychoeducation (ie, individual or group), and, where available, peer support, which have been shown to be impactful and cost-effective.[110,111]

The primary modalities of therapy in bipolar disorders are pharmacotherapeutic, psychosocial, neurostimulatory (eg, electroconvulsive therapy), and lifestyle modification. Pharmacological treatments are the foundation of any treatment plan and have been studied to a greater degree than have other treatment modalities, especially for the treatment of acute mania. However, the exclusion of individuals with bipolar disorders that are most commonly encountered in clinical practice (eg, patients with several comorbidities and suicidality) from most pharmacological studies limits the extrapolation of results from these studies to clinical practice.[112] Multiple regionally, nationally, and internationally authored guidelines for bipolar disorders have been published during the past 5 years.[113–119] In addition, select guidelines have been published that provide decision support for people presenting with mixed depression.[120,121]

The predominance of recommendations based on opinion beyond the first-line treatment phase reflects the paucity of evidence and the absence of empirical guidance for the treatment of treatment-resistant, tertiary patients with comorbidities, and in the treatment of those patients in depressive and maintenance phases of illness.[122] The prevalence of polypharmacy has increased during the past decade in populations of people with bipolar disorders.[123] The foregoing observation invites the need for empirically supported treatment guidelines for patients with bipolar disorders who are prescribed multiple agents.[124] A notable limitation of existing guidelines is the relative absence of substantive input from target stakeholders (ie, people with bipolar disorders).[118] Moreover, there is an absence of rigorous implementation research showing that decision support in clinical practice improves quality indicators, patient-reported outcomes, and the cost-effectiveness of treatment.[104,118]

Computer-based and mobile phone application technologies have promise with respect to screening, diagnosis, symptom monitoring, psychoeducation, and treatment in bipolar disorders. For example, internet-based psychoeducation, and manualised psychotherapeutic interventions that mitigate structural or stigmatic barriers to access are cost-effective, preferred by patients, and, when assisted by clinicians, improve health outcomes.[111] Preliminary evidence suggests that incorporating smartphone technology into the management of bipolar disorders might enhance patient-reported outcomes and the surveillance of symptoms (eg, irritability and mixed symptoms). However, smartphone technology has not yet been empirically shown to reduce recurrence in bipolar disorders or improve patient-reported outcomes.[125–127] Until empirical evidence is available, smartphone technology is considered a promising, rather than an evidence-based, intervention.

Acute mania

Pharmacological treatments are the standard of care for adults experiencing an acute manic episode. Acute mania is a medical emergency that requires urgent treatment to decrease the risk of harm to the patient and others. Antimanic efficacy has been established for multiple agents, but notably for antipsychotics, lithium, divalproex, and carbamazepine (panel 4). Whether an antipsychotic in combination with lithium or divalproex is superior in efficacy to an antipsychotic alone is unknown. Meta-analytic data provides some evidence that antipsychotic agents might be superior to lithium or divalproex with respect to the time to reduce manic symptoms.[128]

Antipsychotic agents are associated with considerable tolerability concerns that are particularly relevant during long-term exposure, including weight gain, metabolic disturbance, prolactin elevation, sedation, somnolence, akathisia, QT interval prolongation corrected for heart rate, and tardive dyskinesia.[129–131] Although each of these tolerability concerns are associated with antipsychotics as a class, there are differences between agents within the class in the type and severity of adverse events reported.

Lithium is a well established antimanic agent that is also capable of attenuating depressive symptoms. Lithium is considered to be the gold standard mood-stabilising agent. Lithium's mood-stabilising properties are especially relevant during the selection of acute treatments because many individuals with bipolar disorders remain on treatment initially prescribed for acute symptoms. Predictors of a good treatment response to lithium include well defined episodes of mania and depression seperated by periods of complete remission, absence of rapid cycling, mixed mood states and psychotic symptoms, family history of bipolar disorders, short illness duration before lithium administration, late age at onset, and low body-mass index.[132] Lithium's anti-suicide effects are a further advantage. Anti-suicide effects are not observed with other agents commonly prescribed to adults with bipolar disorders.[133] Moreover, epidemiological and observational studies have provided preliminary evidence that suggests

Panel 4: **Treatments reported to be efficacious across the various phases of bipolar disorder**

Acute bipolar depression

Treatments approved by the US Food and Drug Administration:

- Cariprazine
- Lurasidone
- Quetiapine
- Olanzapine–fluoxetine

Treatments not approved by the US Food and Drug Administration:

- Lumateperone
- Lithium
- Lamotrigine
- Antidepressants
- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation

Acute mania (all approved by the US Food and Drug Administration, except for*)

- Lithium
- Divalproex
- Carbamazepine
- Aripiprazole
- Asenapine
- Cariprazine
- Haloperidol
- Olanzapine
- Paliperidone*
- Quetiapine
- Risperidone
- Ziprasidone
- Combination treatment with either aripiprazole, asenapine, olanzapine, quetiapine, or risperidone, and lithium or divalproex

Maintenance (all approved by the US Food and Drug Administration, except for*)

- Lithium
- Aripiprazole (oral and long-acting injectable)
- Asenapine
- Lamotrigine
- Paliperidone*
- Quetiapine (adjunctive)
- Olanzapine
- Risperidone (long-acting injectable)

that lithium might reduce the incidence of dementia in people with bipolar disorders.[134,135]

Tolerability concerns with lithium include tremor, polyuria, cognitive impairment, and weight gain. Safety concerns with respect to lithium are the narrow therapeutic index, overdose, hypothyroidism, drug interactions, long-term renal toxicity, and teratogenicity (eg, cardiovascular). Epidemiological studies have reported that the risk of end-stage chronic kidney disease with lithium, although greater than that in the general population, is negligible, possibly because of improved renal monitoring and targeted lithium concentrations (ie, 0·6–0·8 mmol/L).[136]

Although divalproex is efficacious in mania, efficacy in depression and long-term prevention of recurrence has not been well established. In addition, divalproex has many tolerability and safety concerns, including menstrual irregularities in women of reproductive age, an association with polycystic ovarian syndrome, hepatotoxicity, pancreatitis, and teratogenicity. Exposure to divalproex during pregnancy, especially during the first trimester, is associated with a significant dose-dependent risk for major developmental malformations when compared with the risk in a population without exposure (ie, 9·4–11·2% *vs* 2·0–2·5%).[137] The risk for spina bifida with valproate exposure is approximately 1·5–5·0%, which is higher than the risk in the general population (ie, 0·065%). Folate supplementation does not appear to prevent neural tube defects in the pregnancies of women exposed to divalproex.[137] Additional treatment-emergent adverse events with divalproex include tremor, weight gain, sedation, cognitive impairment, and metabolic disruption.

Like divalproex, carbamazepine is effective in acute mania, but there is insufficient evidence showing the acute or long-term prophylactic effects of carbamazepine in bipolar disorders. Additional limitations of carbamazepine are drug–drug interactions due to the ability of carbamazepine to induce its own clearance and the clearance of other medications (ie, substrates of cytochrome P450 3A4), and concerns over tolerability and safety (eg, cognitive impairments, rash, tremors, teratogenicity, Stevens-Johnson syndrome [with an increased risk in Han Chinese carriers of *HLA-B*1502*]). Pre-treatment guidance with pharmacogenetic testing for allelic variants of *HLA-B* has been shown to mitigate risk for Stevens-Johnson Syndrome.[138] Lithium, divalproex, and carbamazepine blood concentrations must be closely monitored when prescribed to individuals with bipolar disorders.

Among people who are insufficiently responsive to pharmacological treatment for mania, electroconvulsive therapy remains an underused treatment option.[139] The evidence supporting the efficacy of other neurostimulation modalities for mania (eg, repetitive transcranial magnetic stimulation) is insufficient.

Clinicians providing care to adults with acute mania should confine their treatment selections to antipsychotics, lithium, divalproex, and carbamazepine. The selection, sequence, and combination of antimanic agents must be tailored to each patient and informed by their illness presentation, previous history, treatment preferences, and comorbidities, acquisition costs, and the availability of safety monitoring.

Acute depression

Pharmacological treatments that are effective for bipolar depression are listed in panel 4. Not all effective agents

are available in most countries and regions globally. Although lithium is recommended across many guidelines as a first-line treatment for bipolar depression, lithium's acute and preventive effects on depressive symptoms are less well established than is lithium's antimanic efficacy.[140,141]

Treatments for bipolar depression are cariprazine, lurasidone, quetiapine, and the combination of olanzapine–fluoxetine. Cariprazine is a partial agonist and antagonist of dopamine and serotonin receptors (formerly described as a second-generation antipsychotic) that has also shown efficacy in the treatment of acute bipolar depression as a monotherapy. Cariprazine has a minimal liability to cause weight gain and does not adversely affect metabolic variables, but is not yet widely available. Lurasidone has not been studied in acute bipolar mania. Lurasidone has a negligible liability to cause weight gain and is not known to adversely affect metabolic homoeostasis. Quetiapine is effective in both bipolar I and bipolar II depression and has been shown to help to prevent recurrence in mania and depression. The limitations of quetiapine and olanzapine–fluoxetine are the considerable propensity for weight gain, metabolic disruption, and sedation.

There is ongoing controversy regarding the safe and appropriate use of antidepressants in bipolar disorders. Antidepressants are associated with treatment-emergent mania, mood destabilisation, the induction of dysphoria, and suicidality in people with bipolar disorders. The risk of treatment-emergent mania in patients with bipolar disorders has been reported to be as high as 30% in retrospective studies, 12% in randomised controlled studies, and 2–6% in studies in which antidepressants were administered in combination with lithium, second-generation antipsychotics, or valproic acid.[142]

The International Society of Bipolar Disorders' consensus statement recommends the use of antidepressants as adjunctive agents in people who have stable, episodic bipolar depression and do not present with rapid cycling, mixed features, a history of previous antidepressant-induced destabilisation, or combinations of these presentations.[143] Antidepressants can be administered adjunctively to mood-stabilising pharmacological agents (eg, lithium, lamotrigine, and second-generation antipsychotics). A small body of evidence indicates that select serotonin reuptake inhibitors (eg, fluoxetine and sertraline), serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine), and norepinephrine and dopamine reuptake inhibitors and releasers (eg, bupropion) can also be used as monotherapy for the acute treatment and maintenance treatment of adults with bipolar II depression.[144,145]

Meta-analytic evidence indicates that response and remission rates to electroconvulsive therapy in the treatment of bipolar depression are similar to the rates reported in major depressive disorder. Individuals with bipolar disorders might require fewer sessions of electroconvulsive therapy to see clinically significant improvements in depressive symptoms when compared with patients with major depressive disorder.[146] However, little rigorous, controlled evidence supports the effects of electroconvulsive therapy in preventing recurrence in people with bipolar disorders. The evidence supporting repetitive transcranial magnetic stimulation is less robust than that supporting electroconvulsive therapy in acute or maintenance treatment.[147–149] Advantages of repetitive transcranial magnetic stimulation over electroconvulsive therapy include better patient acceptability and a lower propensity for cognitive impairment. Despite sequential therapeutic approaches for the treatment of bipolar depression, a large proportion of adults with bipolar disorders manifest treatment-resistant depression.[150]

Maintenance treatment

Few pharmacotherapeutic treatments for bipolar disorders have shown efficacy as maintenance treatments (ie, the prevention of mania and depression in randomised, double-blind, placebo-controlled trials; panel 4).[151] Some agents that are approved in parts of the world as maintenance treatments for bipolar disorders have shown the ability to delay the onset of, and reduce the recurrence of, mania but not depression (eg, risperidone and aripiprazole). Other agents (eg, lamotrigine) have shown efficacy in the maintenance of antidepression, with less efficacy in preventing mania. The enormous gap in the evidence base for maintenance treatments is largely a consequence of the complexity, costs, and ethical concerns in maintaining adults with bipolar disorders on a placebo treatment for multiple years.

Upon the stabilisation of acute episodes of mania or depression, the guiding principle of maintenance pharmacotherapy is that most patients will require multi-year and, in some cases, indefinite therapy. Where possible, limiting exposure to some agents (eg, antipsychotics) because of safety concerns can be attempted by discontinuation of the agent after approximately 6–12 months. However, there is insufficient evidence to guide practitioners as to which agents, if at all, should be discontinued (or added) during the maintenance treatment of a patient in whom the agent is tolerable and safe.

Lithium is an important first-line treatment for bipolar disorders and has shown superiority over divalproex in preventing the recurrence of manic and depressive episodes.[152,153] Evidence of efficacy as maintenance treatments in bipolar disorders exists for quetiapine, and the long-acting, injectable agents, risperidone and aripiprazole. Quetiapine, but not risperidone or aripiprazole, has shown antidepressant efficacy.[118] A separate line of evidence indicates that, like lithium, some long-acting, injectable agents are capable of preventing rehospitalisation in patients with bipolar disorders.[154]

Promotion of patient self-management, primary prevention for psychiatric and medical comorbidity, compliance enhancement strategies, and interventions with psychosocial treatment are crucial elements of care

during maintenance treatment. Manual-based psychosocial treatments (eg, cognitive behavioural therapy) for bipolar disorders delivered during the maintenance phase improve pharmacotherapeutic treatment compliance, reduce affective morbidity, and improve quality of life and function, and should be considered where available. Evidence for the efficacy and cost-effectiveness of individual and group psychoeducation has also been reported for patients with bipolar disorders. Surveillance for suicidality in people with bipolar disorders is a primary therapeutic objective during the acute and maintenance phases.

Cognition

Symptomatic and euthymic individuals, and unaffected first-degree relatives of people with bipolar disorders, show deficits across multiple domains of cognitive function (eg, working memory).[155] During remission, an estimated 10–40% of patients exhibit global cognitive deficits, 29–40% show selective declines in attention and psychomotor speed, and 30–50% present as cognitively intact.[156] Some studies report a subpopulation of people with bipolar disorders who might exhibit progressive, cognitive decline as a function of episode frequency.[157,158]

Factors associated with cognitive impairment in bipolar disorders can be categorised as sociodemographic (eg, age and education), clinical, and treatment-related. For example, individuals with bipolar disorders and a history of psychosis are more likely to exhibit cognitive impairment than are individuals with bipolar disorders who do not have a history of psychosis. This finding might explain the observation that individuals with bipolar I disorder have a greater likelihood of cognitive impairment than do individuals with bipolar II disorder. Other clinical factors include episode frequency and comorbidity. Drug and alcohol misuse and select medical comorbidities (eg, thyroid dysfunction) adversely affect cognitive function in people with bipolar disorders.

***Panel 5*: Treating and preventing cognitive impairment in bipolar disorders**

- Treat symptoms to full remission
- Prevent episode recurrence
- Discontinue dyscognitive medications and substances (eg, benzodiazepines and recreational marijuana)
- Target psychiatric comorbidity (eg, alcohol and substance use and attention-deficit hyperactivity disorder)
- Target medical comorbidity (eg, thyroid disturbance, obesity, and type 2 diabetes)
- Normalise sleep behaviour and chronobiology
- Recommend aerobic and resistance exercise
- Investigational treatments (eg, liraglutide, pramipexole, erythropoietin, cariprazine, and lurasidone)
- Consider neurostimulation (eg, repetitive transcranial magnetic stimulation)
- Attempt cognitive remediation

The dyscognitive effects of obesity in general have been observed, but these effects have also been reported in people with bipolar disorders. The presence of overweight or obesity in people with bipolar disorders is associated with decreased executive functions and processing speed.[159] The bidirectional and complex association between obesity and bipolar disorders is further illustrated by evidence that individuals presenting with first-episode bipolar disorders and lower cognitive performances are at greater risk of subsequent weight gain.[160,161]

Despite the importance of cognition, especially regarding patient-reported outcomes (eg, quality of life and psychosocial function), no treatment has been well established to be efficacious in improving cognition in people with bipolar disorders in large, randomised, placebo-controlled trials.[156,159,162–170] Pragmatic and investigational strategies for the prevention and treatment of cognitive deficits in people with bipolar disorders are presented in panel 5.

Novel treatments for bipolar disorders

Novel treatments for bipolar disorders target disparate effector systems, including molecular targets that participate in neuroplasticity, neurotrophism, apoptosis, inflammation, oxidative and nitrosative stress, mitochondrial function, and metabolic pathways. Examples of such novel treatments are coenzyme Q10, N-acetyl cysteine, statins, non-steroidal anti-inflammatory agents, omega-3 fatty acids, incretin-based therapies, insulin, nitrous oxide, ketamine, prebiotics, probiotics, and antibiotics.[171–174]

Considerable attention is being given to the possibility of altered gut microbial diversity as relevant to the disease process and comorbidity in bipolar disorders. Replicated evidence indicates that adults with bipolar disorders show decreased gut microbial diversity relative to healthy controls or unaffected first-degree relatives.[175,176] Notwithstanding, interventional recommendations with gut microbiota modulators (eg, prebiotics and probiotics) cannot be recommended at present. A promising clinical application is the antibiotic minocycline, which has been reported in open-label trials to attenuate depressive symptoms in people with bipolar disorders and has been evidenced in controlled trials to attenuate depressive symptoms in people with major depressive disorder.[177,178] It should be noted that rigorous randomised controlled trials have not found efficacy for minocycline in the treatment of people with bipolar depression.[75] However, whether the effects of minocycline in patients with bipolar disorders are mediated via the gut microbiome or via other pathways (eg, microglial stabilisation and anti-inflammation) is unknown.

Racemic ketamine has shown efficacy in single dose and repeat dose administration in adults with bipolar disorders.[179] The advantages of ketamine include rapid symptom attenuation, efficacy in treatment-resistant,

severe, and persistent depression, and possible anti-anhedonia and anti-suicide effects.[180] Ketamine does not appear to induce hypomanic, manic, or psychotic symptoms at a rate higher than that of placebo; nevertheless, the absence of safety and efficacy data, and the possibility of misuse, diversion, and gateway activity predicated on ketamine's opioid mechanisms, cannot be ruled out when used in people with bipolar disorders.[181] Preliminary evidence also suggests that intravenous ketamine might reduce suicidality (ie, suicidal ideation) in adults with mood disorders.[182,183]

Meta-analytic evidence for N-acetyl cysteine has been mixed. Moreover, evidence for most anti-inflammatory agents as treatments for bipolar disorders is limited by considerable heterogeneity in trial design and methodology.[184] Preliminary evidence suggests that anticytokine therapy (eg, infliximab) attenuates the severity of depression symptoms in adults with bipolar disorders reporting a history of sexual abuse.[185] Preliminary evidence also suggests that incretin-based therapies might mitigate depression and cognitive symptoms in adults with mood disorders.[182,183,186]

An additional potential therapeutic avenue in bipolar disorders is the targeting of central neurosteroids. The efficacy of intravenous brexanolone, a positive allosteric modulator of γ-aminobutyric-acid (GABA) type A receptors, in post-partum depression suggests potential efficacy for this agent in bipolar depression.[187,188] The availability of an oral formulation of brexanolone and the efficacy of brexanolone in major depressive disorder provides the impetus for further testing of brexanolone in people with bipolar disorders.[189,190]

Chronobiological disturbances are central to the pathogenesis and phenomenology of bipolar disorders.[191] Lithium targets key molecular systems (ie, GSK-3 beta) that are implicated in cellular rhythms and are thought to be relevant to lithium's mechanism of action.[192] Adjunctive bright light therapy (ie, 7000 lx) has shown efficacy in the treatment of adults with bipolar depression without exacerbating hypomanic symptoms and should be considered a treatment alternative when more conventional approaches are insufficient. Hitherto, melatonin-based treatments have not been reported to be efficacious in bipolar disorders; a testable hypothesis is that orexin-based therapies (eg, suvorexant) might be viable therapeutic agents in individuals with mood disorders.[193–195]

Despite the unmet needs in bipolar disorders with existing treatments and the promise of mechanistically dissimilar novel agents, these foregoing investigational agents cannot be considered efficacious or safe in the treatment of bipolar disorders. Moreover, some agents (eg, folic acid) might reduce the efficacy of mood stabilisers.[196,197] Nevertheless, novel targets are being exploited in therapeutic research to improve upon existing treatments for bipolar disorders and to identify novel approaches to modify disease.

Conclusion

The overarching unmet needs in bipolar disorders are accurate and timely diagnosis and the prompt implementation of effective therapies. An implementation gap exists; most individuals with bipolar disorders do not receive integrated, best practice care. Closing this gap provides the greatest opportunity to reduce morbidity and mortality in people with bipolar disorders and is important for both mental health and concurrent physical comorbidity. Notwithstanding the requirement for hypomania or mania in the diagnosis of bipolar disorders, the past decade of research has convincingly suggested that enduring deficits in general cognition, cognitive emotional processing, reward-based decision making, and chronobiology are the principal mediators of health outcomes. Domain-based pathology manifests more typically as depressive and mixed symptomatology.

The availability of so-called rapid-onset treatments (eg, ketamine) and treatments that could mitigate suicidality is crucial to clinical settings. The next decade will see the testing of mechanistically novel agents for bipolar disorders targeting glutamate, GABAergic systems, immune-inflammatory systems, metabolic pathways, mitochondrial function, orexin systems, and neurotrophic and neuroplasticity intracellular cascades. The use of technology awaits empirical evidence on its effects on health outcomes and cost in bipolar disorders, but has promise for the assessment and monitoring of phenomenology and in facilitating self-management. The prevention of bipolar disorders is a viable objective. Toward this aim, targeting effectors via public health initiatives (eg, reducing obesity and increasing exercise), psychosocial interventions (eg, cognitive remediation), and pharmacotherapeutic strategies (eg, anti-inflammatory therapies) are areas for future research.

Contributors

RSM conceptualised the Seminar, created the first draft, and was involved in substantive edits. MB, EB, BIG, CL-J, LVK, GSM, AAN, JDR, AM, EV, MV, AYH, and RBM provided substantial input to the content, the emphasis, and the key messages of the manuscript, and were involved in substantive edits.

Declaration of interests

RSM has received grant support from the Stanley Medical Research Institute and the Canadian Institutes of Health Research/the Global Alliance for Chronic Disease/Chinese National Natural Research Foundation, has received speaker fees from Lundbeck, Janssen, Shire, Purdue, Pfizer, Otsuka, Allergan, Takeda, Neurocrine, Sunovion, Intra-cellular, Alkermes, and Minerva, and is the chief executive officer of Champignon. MB is supported by a National Health and Medical Research Council senior principal research fellowship (1059660 and APP1156072), has received grants and research support from the National Institutes of Health, the Cooperative Research Centre, the Simons Autism Foundation, the Cancer Council of Victoria, the Stanley Medical Research Foundation, the Medical Benefits Fund, the National Health and Medical Research Council, the Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, the Meat and Livestock Board, Woolworths, Avant, and the Harry Windsor Foundation, has been a speaker for AstraZeneca, Lundbeck, Merck, and Pfizer, and has served as a consultant to Allergan, AstraZeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer, and Servier. EB has received

grant support from the Sao Paulo Research Foundation, the Brazilian National Council for Scientific and Technological Development, Coordination for the Improvement of Higher Education Personnel, the L'Oreal For Women in Science Award, and the SouthEastern Ontario Academic Medical Association, Harry Botterell Foundation for Neurological Sciences Dr James B Howe Endowment Fund, the Violet E Powell Endowed Funds, the Faculty of Health Sciences at Queen's University, internal grants from the Department of Psychiatry and Centre for Neuroscience Studies, Queen's University, and has received honoraria as a speaker and an advisory board member from Daiichi-Sankyo. BIG has received grants or research support from the Brain and Behavior Research Foundation (NARSAD), Brain Canada, the Canadian Institutes of Health Research, the Heart and Stroke Foundation, the National Institute of Mental Health, the Ontario Ministry of Research and Innovation, and the Department of Psychiatry (University of Toronto). LVK has been a consultant for Lundbeck between 2017 and 2020. JVR has received grant support from the Canadian Cancer Society and the Department of Psychiatry (University of Toronto), and is a subinvestigator on a study of the safety and efficacy of psilocybin in participants with treatment-resistant depression, which is sponsored by COMPASS. EV has received grants from, and has served as a consultant, adviser, or continuing medical education speaker for, AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Galenica, Janssen, Lundbeck, Novartis, Otsuka, Sage, Sanofi-Aventis, and Takeda. MV, within 2017–20, has been a speaker for Lundbeck and Sunovion, and has served as a consultant for Janssen. AHY is employed by King's College London, is an honorary consultant for South London and Maudsley National Health Service Foundation Trust, declares paid lectures and a presence on advisory boards for AstraZeneca, Eli Lilly, Lundbeck, SAGE, Sunovion, Servier, Livanova, Janssen, Allergan, and Bionomics, with drugs used in affective and related disorders, is a consultant for Johnson & Johnson and Livanova, is a principal investigator in the RESTORE-LIFE vagus nerve stimulation registry study funded by LivaNova, in the ESKETINTRD3004 study (an open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression), in a study on the effects of psilocybin on cognitive function in healthy participants, and in a study on the safety and efficacy of psilocybin in participants with treatment-resistant depression, has no shareholdings in pharmaceutical companies, and is funded by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London. RBM has received grants or research support from the Academic Scholar Award, the Department of Psychiatry (University of Toronto), and the Canadian Institutes of Health Research. GSM has received grant or research support from Australian Rotary Health, the National Health and Medical Research Council, New South Wales Ministry of Health, Ramsay Health, University of Sydney, The American Foundation for Suciide Prevention, AstraZeneca, Eli Lilly and Co, Organon, Pfizer, Servier, and Wyeth, has been a speaker for Abbott, AstraZeneca, Eli Lilly and Co, Janssen Cilag, Lundbeck, Pfizer, Ranbaxy, Servier, and Wyeth, and has been a consultant for AstraZeneca, Eli Lilly and Co, Janssen Cilag, Lundbeck, and Servier. All other authors declare no competing interests.

Acknowledgments

EV thanks the Spanish Ministry of Science and Innovation (PI15/00283 and PI18/00805) integrated into the National I+D+I Plan (cofunded by ISCIII-FEDER, CIBERSAM, and the Comissionate for Universities) and Research of the Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365) and the project SLT006/17/00357, from PERIS 2016–20 (Health Department; CERCA Programme, Generalitat de Catalunya). The views expressed in this Seminar are those of the authors and are not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

References

1 Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; **68:** 241–51.

2 Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *Int J Epidemiol* 2014; **43:** 476–93.

3 Godman B, Grobler C, Van-De-Lisle M, et al. Pharmacotherapeutic interventions for bipolar disorder type II: addressing multiple symptoms and approaches with a particular emphasis on strategies in lower and middle-income countries. *Expert Opin Pharmacother* 2019; **20:** 2237–55.

4 Sentissi O, Popovic D, Moeglin C, et al. Predominant polarity in bipolar disorder patients: the COPE bipolar sample. *J Affect Disord* 2019; **250:** 43–50.

5 Nowrouzi B, McIntyre RS, MacQueen G, et al. Admixture analysis of age at onset in first episode bipolar disorder. *J Affect Disord* 2016; **201:** 88–94.

6 Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry* 2007; **64:** 1032–39.

7 Jamison KR. Great wits and madness: more near allied? *Br J Psychiatry* 2011; **199:** 351–52.

8 Cloutier M, Greene M, Guerin A, Touya M, Wu E. The economic burden of bipolar I disorder in the United States in 2015. *J Affect Disord* 2018; **226:** 45–51.

9 Kleine-Budde K, Touil E, Moock J, Bramesfeld A, Kawohl W, Rössler W. Cost of illness for bipolar disorder: a systematic review of the economic burden. *Bipolar Disord* 2014; **16:** 337–53.

10 Jin H, McCrone P. Cost-of-illness studies for bipolar disorder: systematic review of international studies. *Pharmacoeconomics* 2015; **33:** 341–53.

11 Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 2011; **131:** 101–04.

12 Osby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* 2001; **58:** 844–50.

13 Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. *Bipolar Disord* 2015; **17:** 543–48.

14 Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *Br J Psychiatry* 2017; **211:** 175–81.

15 Staudt Hansen P, Frahm Laursen M, Grøntved S, Puggard Vogt Straszek S, Licht RW, Nielsen RE. Increasing mortality gap for patients diagnosed with bipolar disorder—a nationwide study with 20 years of follow-up. *Bipolar Disord* 2019; **21:** 270–75.

16 Lomholt LH, Andersen DV, Sejrsgaard-Jacobsen C, et al. Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: a nationwide study with 20 years of follow-up. *Int J Bipolar Disord* 2019; **7:** 6.

17 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:** 142–47.

18 Hällgren J, Ösby U, Westman J, Gissler M. Mortality trends in external causes of death in people with mental health disorders in Sweden, 1987–2010. *Scand J Public Health* 2019; **47:** 121–26.

19 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.

20 Tietbohl-Santos B, Chiamenti P, Librenza-Garcia D, et al. Risk factors for suicidality in patients with panic disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2019; **105:** 34–38.

21 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.

22 Malhi GS, Irwin L, Hamilton A, et al. Modelling mood disorders: an ACE solution? *Bipolar Disord* 2018; **20** (suppl 2)**:** 4–16.

23 Tondo L, Vázquez GH, Pinna M, Vaccotto PA, Baldessarini RJ. Characteristics of depressive and bipolar disorder patients with mixed features. *Acta Psychiatr Scand* 2018; **138:** 243–52.

24 McIntyre RS. Mixed features and mixed states in psychiatry: from calculus to geometry. *CNS Spectr* 2017; **22:** 116–17.

25 Shim IH, Bae DS, Bahk W-M. Anxiety or agitation in mood disorder with mixed features: a review with a focus on validity as a dimensional criterion. *Ann Clin Psychiatry* 2016; **28:** 213–20.

26 Perugi G, Angst J, Azorin JM, et al. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry* 2015; **76:** e351–58.

27 Malhi GS, Das P, Gessler D, Outhred T, Fritz K. The mixed features of DSM-5. *Aust N Z J Psychiatry* 2015; **49:** 842–43.

28 Malhi GS, Fritz K, Allwang C, et al. Agitation for recognition by DSM-5 mixed features specifier signals fatigue? *Aust N Z J Psychiatry* 2015; **49:** 499–501.

29 Brancati GE, Vieta E, Azorin JM, et al. The role of overlapping excitatory symptoms in major depression: are they relevant for the diagnosis of mixed state? *J Psychiatr Res* 2019; **115:** 151–57.

30 Perugi G, Pacchiarotti I, Mainardi C, et al. Patterns of response to antidepressants in major depressive disorder: drug resistance or worsening of depression are associated with a bipolar diathesis. *Eur Neuropsychopharmacol* 2019; **29:** 825–34.

31 Malhi GS, Fritz K, Elangovan P, Irwin L. Mixed states: modelling and management. *CNS Drugs* 2019; **33:** 301–13.

32 McIntyre RS, Calabrese JR. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. *Curr Med Res Opin* 2019; **35:** 1993–2005.

33 Messer T, Lammers G, Müller-Siecheneder F, Schmidt R-F, Latifi S. Substance abuse in patients with bipolar disorder: a systematic review and meta-analysis. *Psychiatry Res* 2017; **253:** 338–50.

34 Cawkwell PB, Bolton KW, Karmacharya R, Öngür D, Shinn AK. Two-year diagnostic stability in a real-world sample of individuals with early psychosis. *Early Interv Psychiatry* 2020; published online Feb 10. https://doi.org.10.1111/eip.12930.

35 Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* 2011; **168:** 40–48.

36 Perugi G, Angst J, Azorin JM, et al. Relationships between mixed features and borderline personality disorder in 2811 patients with major depressive episode. *Acta Psychiatr Scand* 2016; **133:** 133–43.

37 Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. *Can J Psychiatry* 2017; **62:** 247–58.

38 Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* 2005; **84:** 149–57.

39 Kessing LV, Willer I, Andersen PK, Bukh JD. Rate and predictors of conversion from unipolar to bipolar disorder: a systematic review and meta-analysis. *Bipolar Disord* 2017; **19:** 324–35.

40 Ratheesh A, Davey C, Hetrick S, et al. A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. *Acta Psychiatr Scand* 2017; **135:** 273–84.

41 Li C-T, Bai YM, Huang YL, et al. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. *Br J Psychiatry* 2012; **200:** 45–51.

42 Hirschfeld RMA, 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.

43 Youngstrom EA, Egerton GA, Genzlinger J, Freeman LK, Rizvi SH, Van Meter A. Improving the global identification of bipolar spectrum disorders: meta-analysis of the diagnostic accuracy of checklists. *Psychol Bull* 2018; **144:** 315–42.

44 Wang Y-Y, Xu DD, Liu R, et al. Comparison of the screening ability between the 32-item Hypomania Checklist (HCL-32) and the Mood Disorder Questionnaire (MDQ) for bipolar disorder: a meta-analysis and systematic review. *Psychiatry Res* 2019; **273:** 461–66.

45 Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; **64:** 543–52.

46 Sylvia LG, Shelton RC, Kemp DE, et al. Medical burden in bipolar disorder: findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). *Bipolar Disord* 2015; **17:** 212–23.

47 McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol* 2004; **19:** 369–86.

48 Vaccarino SR, Rajji TK, Gildengers AG, et al. Allostatic load but not medical burden predicts memory performance in late-life bipolar disorder. *Int J Geriatr Psychiatry* 2018; **33:** 546–52.

49 Kapczinski NS, Mwangi B, Cassidy RM, et al. Neuroprogression and illness trajectories in bipolar disorder. *Expert Rev Neurother* 2017; **17:** 277–85.

50 Yapici Eser H, Kacar AS, Kilciksiz CM, Yalçinay-Inan M, Ongur D. Prevalence and associated features of anxiety disorder comorbidity in bipolar disorder: a meta-analysis and meta-regression study. *Front Psychiatry* 2018; **9:** 229.

51 Onyeka IN, Collier Høegh M, Nåheim Eien EM, Nwaru BI, Melle I. Comorbidity of physical disorders among patients with severe mental illness with and without substance use disorders: a systematic review and meta-analysis. *J Dual Diagn* 2019; **15:** 192–206.

52 McElroy SL, Winham SJ, Cuellar-Barboza AB, et al. Bipolar disorder with binge eating behavior: a genome-wide association study implicates PRR5-ARHGAP8. *Transl Psychiatry* 2018; **8:** 40.

53 McIntyre RS, Correll C. Predicting and preventing bipolar disorder: the need to fundamentally advance the strategic approach. *Bipolar Disord* 2014; **16:** 451–54.

54 Coello K, Kjærstad HL, Stanislaus S, et al. Thirty-year cardiovascular risk score in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. *Aust N Z J Psychiatry* 2019; **53:** 651–62.

55 Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2015; **132:** 965–86.

56 Petri E, Bacci O, Barbuti M, et al. Obesity in patients with major depression is related to bipolarity and mixed features: evidence from the BRIDGE-II-Mix study. *Bipolar Disord* 2017; **19:** 458–64.

57 Bora E, Yucel M, Fornito A, Berk M, Pantelis C. Major psychoses with mixed psychotic and mood symptoms: are mixed psychoses associated with different neurobiological markers? *Acta Psychiatr Scand* 2008; **118:** 172–87.

58 Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, Hedman AM. A population-based heritability estimate of bipolar disorder—in a Swedish twin sample. *Psychiatry Res* 2019; **278:** 180–87.

59 Fabbri C. The role of genetics in bipolar disorder. *Curr Top Behav Neurosci* 2020; published online August 7. https://doi.org/10.1007/7854_2020_153.

60 Barnett JH, Smoller JW. The genetics of bipolar disorder. *Neuroscience* 2009; **164:** 331–43.

61 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.

62 Chen DT, Jiang X, Akula N, et al. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol Psychiatry* 2013; **18:** 195–205.

63 Smeland OB, et al. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Mol Psychiatry* 2020; **25:** 844–53.

64 Wang M, Zhang L, Gage FH. Modeling neuropsychiatric disorders using human induced pluripotent stem cells. *Protein Cell* 2020; **11:** 45–59.

65 Andreazza AC, Duong A, Young LT. Bipolar disorder as a mitochondrial disease. *Biol Psychiatry* 2018; **83:** 720–21.

66 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.

67 Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res* 2014; **218:** 61–68.

68 Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry* 2009; **70:** 1078–90.

69 Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2014; **53:** 23–34.

70 Dargél AA, Godin O, Kapczinski F, Kupfer DJ, Leboyer M. C-reactive protein alterations in bipolar disorder: a meta-analysis. *J Clin Psychiatry* 2015; **76:** 142–50.

71 Rowland T, Perry BI, Upthegrove R, et al. Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: systematic review and meta-analyses. *Br J Psychiatry* 2018; **213:** 514–25.

72 Hamdani N, Bengoufa D, Godin O, et al. Immunoglobulin sub-class distribution in bipolar disorder and schizophrenia: potential relationship with latent *Toxoplasma gondii* infection. *BMC Psychiatry* 2018; **18:** 239.

73 Hamdani N, Daban-Huard C, Godin O, et al. Effects of cumulative Herpesviridae and *Toxoplasma gondii* infections on cognitive function in healthy, bipolar, and schizophrenia subjects. *J Clin Psychiatry* 2017; **78:** e18–27.

74 Frye MA, Coombes BJ, McElroy SL, et al. Association of *Cytomegalovirus* and *Toxoplasma gondii* antibody titers with bipolar disorder. *JAMA Psychiatry* 2019; **76:** 1285–93.

75 Husain MI, Chaudhry IB, Khoso AB, et al. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. *Lancet Psychiatry* 2020; **7:** 515–27.

76 McIntyre RS, Danilewitz M, Liauw SS, et al. Bipolar disorder and metabolic syndrome: an international perspective. *J Affect Disord* 2010; **126:** 366–87.

77 Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 2015; **14:** 339–47.

78 McIntyre RS, Rong C, Mansur RB, Brietzke E. Does obesity and diabetes mellitus metastasize to the brain? "Metaboptosis" and implications for drug discovery and development. *CNS Spectr* 2019; **24:** 467–69.

79 Hajek T, Calkin C, Blagdon R, Slaney C, Alda M. Type 2 diabetes mellitus: a potentially modifiable risk factor for neurochemical brain changes in bipolar disorders. *Biol Psychiatry* 2015; **77:** 295–303.

80 Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. *Neuropsychopharmacology* 2014; **39:** 2910–18.

81 da Silva EG, Pfaffenseller B, Walz J, et al. Peripheral insulin-like growth factor 1 in bipolar disorder. *Psychiatry Res* 2017; **250:** 30–34.

82 Milanesi E, Zanardini R, Rosso G, et al. Insulin-like growth factor binding protein 2 in bipolar disorder: an expression study in peripheral tissues. *World J Biol Psychiatry* 2018; **19:** 610–18.

83 Alageel A, Tomasi J, Tersigni C, et al. Evidence supporting a mechanistic role of sirtuins in mood and metabolic disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **86:** 95–101.

84 Pinto JV, Passos IC, Gomes F, et al. Peripheral biomarker signatures of bipolar disorder and schizophrenia: a machine learning approach. *Schizophr Res* 2017; **188:** 182–84.

85 Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. *World Psychiatry* 2017; **16:** 236–44.

86 Miklowitz DJ, Scott J. Psychosocial treatments for bipolar disorder: cost-effectiveness, mediating mechanisms, and future directions. *Bipolar Disord* 2009; **11** (suppl 2)**:** 110–22.

87 Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord* 2011; **13:** 87–98.

88 Tremain H, Fletcher K, Scott J, McEnery C, Berk M, Murray G. Does stage of illness influence recovery-focused outcomes after psychological treatment in bipolar disorder? A systematic review protocol. *Syst Rev* 2019; **8:** 125.

89 Kessing LV, Vradi E, Andersen PK. Starting lithium prophylaxis early v. late in bipolar disorder. *Br J Psychiatry* 2014; **205:** 214–20.

90 Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* 2016; **387:** 1561–72.

91 Valli I, Fabbri C, Young AH. Uncovering neurodevelopmental features in bipolar affective disorder. *Br J Psychiatry* 2019; **215:** 383–85.

92 Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry* 2005; **186:** 121–25.

93 Post RM, Altshuler LL, Kupka R, et al. Age of onset of bipolar disorder: combined effect of childhood adversity and familial loading of psychiatric disorders. *J Psychiatr Res* 2016; **81:** 63–70.

94 Post RM, Altshuler LL, Kupka R, et al. Verbal abuse, like physical and sexual abuse, in childhood is associated with an earlier onset and more difficult course of bipolar disorder. *Bipolar Disord* 2015; **17:** 323–30.

95 Leclerc E, Mansur RB, Grassi-Oliveira R, et al. The differential association between history of childhood sexual abuse and body mass index in early and late stages of bipolar disorder. *J Affect Disord* 2018; **227:** 214–18.

96 McIntyre RS, Soczynska JK, Liauw SS, et al. The association between childhood adversity and components of metabolic syndrome in adults with mood disorders: results from the international mood disorders collaborative project. *Int J Psychiatry Med* 2012; **43:** 165–77.

97 Al-Haddad BJS, Oler E, Armistead B, et al. The fetal origins of mental illness. *Am J Obstet Gynecol* 2019; **221:** 549–62.

98 Goodwin FK, Jamison KR. Manic-depressive illness. Bipolar disorders and recurrent depression. New York, NY: Oxford University Press, 2007.

99 Gignac A, McGirr A, Lam RW, Yatham LN. Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. *J Clin Psychiatry* 2015; **76:** 1241–48.

100 Kessing LV, Andersen PK, Vinberg M. Risk of recurrence after a single manic or mixed episode—a systematic review and meta-analysis. *Bipolar Disord* 2018; **20:** 9–17.

101 Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am J Psychiatry* 2000; **157:** 220–28.

102 Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br J Psychiatry* 2013; **202:** 212–19.

103 Martin JL, Lowrie R, McConnachie A, et al. Physical health indicators in major mental illness: data from the Quality and Outcome Framework in the UK. *Lancet* 2015; **385** (suppl 1)**:** S61 (abstr).

104 Daivadanam M, Ingram M, Sidney Annerstedt K, et al. The role of context in implementation research for non-communicable diseases: answering the "how-to" dilemma. *PLoS One* 2019; **14:** e0214454.

105 National Institutes of Health. Implementation science news, resources and funding for global health researchers. https://www.fic.nih.gov/researchtopics/pages/implementationscience.aspx (accessed June 25, 2020).

106 Hurst JR, Dickhaus J, Maulik PK, et al. Global Alliance for Chronic Disease researchers' statement on multimorbidity. *Lancet Glob Health* 2018; **6:** e1270–71.

107 Vancampfort D, Firth J, Schuch FB, et al. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. *World Psychiatry* 2017; **16:** 308–15.

108 Li X-H, An FR, Ungvari GS, et al. Prevalence of smoking in patients with bipolar disorder, major depressive disorder and schizophrenia and their relationships with quality of life. *Sci Rep* 2017; **7:** 8430.

109 Subramaniapillai M, Arbour-Nicitopoulos K, Duncan M, et al. Physical activity preferences of individuals diagnosed with schizophrenia or bipolar disorder. *BMC Res Notes* 2016; **9:** 340.

110 Soo SA, Zhang ZW, Khong SJ, et al. Randomized controlled trials of psychoeducation modalities in the management of bipolar disorder: a systematic review. *J Clin Psychiatry* 2018; **79:** 17r11750.

111 Rosenblat JD, Simon GE, Sachs GS, et al. Frequency of use and perceived helpfulness of wellness strategies for bipolar and unipolar depression. *Ann Clin Psychiatry* 2018; **30:** 296–304.

112 Rosenblat JD, Simon GE, Sachs GS, et al. Treatment effectiveness and tolerability outcomes that are most important to individuals with bipolar and unipolar depression. *J Affect Disord* 2019; **243:** 116–20.

113 Fountoulakis KN, Grunze H, Vieta E, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. *Int J Neuropsychopharmacol* 2017; **20:** 180–95.

114 Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; **20:** 97–170.

115 Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2016; **30:** 495–553.

116 National Collaborating Centre for Mental Health (UK). Bipolar disorder: the NICE guideline on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. London: The British Psychological Society and The Royal College of Psychiatrists, 2018.

117 Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry* 2018; **19:** 2–58.

118 Ostacher MJ, Tandon R, Suppes T. Florida best practice psychotherapeutic medication guidelines for adults with bipolar disorder: a novel, practical, patient-centered guide for clinicians. *J Clin Psychiatry* 2016; **77:** 920–26.

119 Malhi GS, Outhred T, Morris G, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: bipolar disorder summary. *Med J Aust* 2018; **208:** 219–25.

120 Stahl SM, Morrissette DA, Faedda G, et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr* 2017; **22:** 203–19.

121 McIntyre RS, Suppes T, Tandon R, Ostacher M. Florida best practice psychotherapeutic medication guidelines for adults with major depressive disorder. *J Clin Psychiatry* 2017; **78:** 703–13.

122 Post RM, Yatham LN, Vieta E, Berk M, Nierenberg AA. Beyond evidence-based treatment of bipolar disorder: rational pragmatic approaches to management. *Bipolar Disord* 2019; **21:** 650–59.

123 Kessing LV, Vradi E, Andersen PK. Nationwide and population-based prescription patterns in bipolar disorder. *Bipolar Disord* 2016; **18:** 174–82.

124 Golden JC, Goethe JW, Woolley SB. Complex psychotropic polypharmacy in bipolar disorder across varying mood polarities: a prospective cohort study of 2712 inpatients. *J Affect Disord* 2017; **221:** 6–10.

125 Faurholt-Jepsen M, Frost M, Busk J, et al. Is smartphone-based mood instability associated with stress, quality of life, and functioning in bipolar disorder? *Bipolar Disord* 2019; **21:** 611–20.

126 Nierenberg AA, Rakhilin M, Deckersbach T. Objective smartphone data as a potential diagnostic marker of bipolar disorder. *Aust N Z J Psychiatry* 2019; **53:** 171–72.

127 Faurholt-Jepsen M, Frost M, Christensen EM, Bardram JE, Vinberg M, Kessing LV. The association between mixed symptoms, irritability and functioning measured using smartphones in bipolar disorder. *Acta Psychiatr Scand* 2019; **139:** 443–53.

128 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.

129 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.

130 Demyttenaere K, Detraux J, Racagni G, Vansteelandt K. Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis. *CNS Drugs* 2019; **33:** 549–66.

131 Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry* 2018; **17:** 330–40.

132 Hui TP, Kandola A, Shen L, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. *Acta Psychiatr Scand* 2019; **140:** 94–115.

133 Chen T-Y, Kamali M, Chu CS, et al. Divalproex and its effect on suicide risk in bipolar disorder: a systematic review and meta-analysis of multinational observational studies. *J Affect Disord* 2019; **245:** 812–18.

134 Hampel H, Lista S, Mango D, et al. Lithium as a treatment for Alzheimer's disease: the systems pharmacology perspective. *J Alzheimers Dis* 2019; **69:** 615–29.

135 Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? *Bipolar Disord* 2010; **12:** 87–94.

136 Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry* 2015; **72:** 1182–91.

137 Patel N, Viguera AC, Baldessarini RJ. Mood-stabilizing anticonvulsants, spina bifida, and folate supplementation: commentary. *J Clin Psychopharmacol* 2018; **38:** 7–10.

138 Chouchi M, Kaabachi W, Tizaoui K, Daghfous R, Aidli SE, Hila L. The HLA-B*15:02 polymorphism and Tegretol-induced serious cutaneous reactions in epilepsy: an updated systematic review and meta-analysis. *Rev Neurol (Paris)* 2018; **174:** 278–91.

139 Perugi G, Medda P, Barbuti M, Novi M, Tripodi B. The role of electroconvulsive therapy in the treatment of severe bipolar mixed state. *Psychiatr Clin North Am* 2020; **43:** 187–97.

140 Manchia M, Rybakowski JK, Sani G, et al. Lithium and bipolar depression. *Bipolar Disord* 2019; **21:** 458–59.

141 Kelly T. Lithium and the Woozle effect. *Bipolar Disord* 2019; **21:** 302–08.

142 Fornaro M, Anastasia A, Novello S, et al. Incidence, prevalence and clinical correlates of antidepressant-emergent mania in bipolar depression: a systematic review and meta-analysis. *Bipolar Disord* 2018; **20:** 195–227.

143 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.

144 Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry* 2011; **72:** 156–67.

145 Altshuler LL, Sugar CA, McElroy SL, et al. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *Am J Psychiatry* 2017; **174:** 266–76.

146 Bahji A, Hawken ER, Sepehry AA, Cabrera CA, Vazquez G. ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression. *Acta Psychiatr Scand* 2018; **20:** 539.

147 Rachid F. Repetitive transcranial magnetic stimulation and treatment-emergent mania and hypomania: a review of the literature. *J Psychiatr Pract* 2017; **23:** 150–59.

148 Myczkowski ML, Fernandes A, Moreno M, et al. Cognitive outcomes of TMS treatment in bipolar depression: safety data from a randomized controlled trial. *J Affect Disord* 2018; **235:** 20–26.

149 Yang L-L, Zhao D, Kong LL, et al. High-frequency repetitive transcranial magnetic stimulation (rTMS) improves neurocognitive function in bipolar disorder. *J Affect Disord* 2019; **246:** 851–56.

150 Hidalgo-Mazzei D, Berk M, Cipriani A, et al. Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. *Br J Psychiatry* 2019; **214:** 27–35.

151 Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder—a systematic review and meta-analysis. *J Affect Disord* 2017; **213:** 138–50.

152 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:** 351–59.

153 Ketter TA, Calabrese JR. Stabilization of mood from below versus above baseline in bipolar disorder: a new nomenclature. *J Clin Psychiatry* 2002; **63:** 146–51.

154 Lähteenvuo M, Tanskanen A, Taipale H, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry* 2018; **75:** 347–55.

155 Matsubara T, Matsuo K, Harada K, et al. Distinct and shared endophenotypes of neural substrates in bipolar and major depressive disorders. *PLoS One* 2016; **11:** e0168493.

156 Miskowiak KW, Burdick KE, Martinez-Aran A, et al. Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. *Bipolar Disord* 2017; **19:** 614–26.

157 Kessing LV, Miskowiak K. Does cognitive dysfunction in bipolar disorder qualify as a diagnostic intermediate phenotype?—a perspective paper. *Front Psychiatry* 2018; **9:** 490.

158 Burdick KE, Millett CE, Bonnín CDM, et al. The International Consortium Investigating Neurocognition in Bipolar Disorder (ICONIC-BD). *Bipolar Disord* 2019; **21:** 6–10.

159 Bora E, McIntyre RS, Ozerdem A. Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review. *Psychol Med* 2019; **49:** 738–49.

160 Bond DJ, Torres IJ, Lee SS, et al. Lower cognitive functioning as a predictor of weight gain in bipolar disorder: a 12-month study. *Acta Psychiatr Scand* 2017; **135:** 239–49.

161 McIntyre RS. Is obesity changing the phenotype of bipolar disorder from predominately euphoric toward mixed presentations? *Bipolar Disord* 2018; **20:** 685–86.

162 Mason L, O'Sullivan N, Montaldi D, Bentall RP, El-Deredy W. Decision-making and trait impulsivity in bipolar disorder are associated with reduced prefrontal regulation of striatal reward valuation. *Brain* 2014; **137:** 2346–55.

163 Kirschner M, et al. Shared and dissociable features of apathy and reward system dysfunction in bipolar I disorder and schizophrenia. *Psychol Med* 2020; **50:** 935–47.

164 Dutra SJ, Man V, Kober H, Cunningham WA, Gruber J. Disrupted cortico-limbic connectivity during reward processing in remitted bipolar I disorder. *Bipolar Disord* 2017; **19:** 661–75.

165 Miskowiak KW, Carvalho AF, Vieta E, Kessing LV. Cognitive enhancement treatments for bipolar disorder: a systematic review and methodological recommendations. *Eur Neuropsychopharmacol* 2016; **26:** 1541–61.

166 Viktorin A, Rydén E, Thase ME, et al. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. *Am J Psychiatry* 2017; **174:** 341–48.

167 Hollis C, Chen Q, Chang Z, et al. Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study. *Lancet Psychiatry* 2019; **6:** 651–58.

168 Łojko D, Stelmach-Mardas M, Suwalska A. Diet quality and eating patterns in euthymic bipolar patients. *Eur Rev Med Pharmacol Sci* 2019; **23:** 1221–38.

169 Subramaniapillai M, Mansur RB, Zuckerman H, et al. Association between cognitive function and performance on effort based decision making in patients with major depressive disorder treated with Vortioxetine. *Compr Psychiatry* 2019; **94:** 152113.

170 McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 2014; **17:** 1557–67.

171 Henter ID, de Sousa RT, Zarate CA Jr. Glutamatergic modulators in depression. *Harv Rev Psychiatry* 2018; **26:** 307–19.

172 Mansur RB, Zugman A, Ahmed J, et al. Treatment with a GLP-1R agonist over four weeks promotes weight loss-moderated changes in frontal-striatal brain structures in individuals with mood disorders. *Eur Neuropsychopharmacol* 2017; **27:** 1153–62.

173 Rutkofsky IH, Khan AS, Sahito S, Kumar V. The psychoneuroimmunological role of omega-3 polyunsaturated fatty acids in major depressive disorder and bipolar disorder. *Adv Mind Body Med* 2017; **31:** 8–16.

174 Saunders EFH, Ramsden CE, Sherazy MS, Gelenberg AJ, Davis JM, Rapoport SI. Omega-3 and omega-6 polyunsaturated fatty acids in bipolar disorder: a review of biomarker and treatment studies. *J Clin Psychiatry* 2016; **77:** e1301–08.

175 Coello K, Hansen TH, Sørensen N, et al. Gut microbiota composition in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. *Brain Behav Immun* 2019; **75:** 112–18.

176 McIntyre RS, Subramaniapillai M, Shekotikhina M, et al. Characterizing the gut microbiota in adults with bipolar disorder: a pilot study. *Nutr Neurosci* 2019; published online May 28. https://doi.org/10.1080/1028415X.2019.1612555.

177 Husain MI, Chaudhry IB, Husain N, et al. Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial. *J Psychopharmacol* 2017; **31:** 1166–75.

178 Rosenblat JD, McIntyre RS. Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *J Affect Disord* 2018; **227:** 219–25.

179 McIntyre RS, Lipsitz O, Rodrigues NB. The effectiveness of ketamine on anxiety, irritability, and agitation: implications for treating mixed features in adults with major depressive or bipolar disorder. *Bipolar Disord* 2020; published online May 13. https://doi.org/10.1111/bdi.12941.

180 Rybakowski JK, Permoda-Osip A, Bartkowska-Sniatkowska A. Ketamine augmentation rapidly improves depression scores in inpatients with treatment-resistant bipolar depression. *Int J Psychiatry Clin Pract* 2017; **21:** 99–103.

181 Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* 2012; **71:** 939–46.

182 Lee Y, Syeda K, Maruschak NA, et al. A new perspective on the anti-suicide effects with ketamine treatment: a procognitive effect. *J Clin Psychopharmacol* 2016; **36:** 50–56.

183 Dakwar E, Nunes EV, Hart CL, et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatry* 2019; **176:** 923–30.

184 Zheng W, Zhang QE, Cai DB, et al. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. *Acta Psychiatr Scand* 2018; **137:** 391–400.

185 McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar i/ii depression: a randomized clinical trial. *JAMA Psychiatry* 2019; **76:** 783.

186 Mansur RB, Ahmed J, Cha DS, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: a pilot, open-label study. *J Affect Disord* 2017; **207:** 114–20.

187 Brown ES, Park J, Marx CE, et al. A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. *Neuropsychopharmacology* 2014; **39:** 2867–73.

188 Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018; **392:** 1058–70.

189 Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. *N Engl J Med* 2019; **381:** 903–11.

190 Youssef NA, Bradford DW, Kilts JD, et al. Exploratory investigation of biomarker candidates for suicide in schizophrenia and bipolar disorder. *Crisis* 2015; **36:** 46–54.

191 Grigolon RB, Trevizol AP, Cerqueira RO, et al. Hypersomnia and bipolar disorder: a systematic review and meta-analysis of proportion. *J Affect Disord* 2019; **246:** 659–66.

192 Moreira J, Geoffroy PA. Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. *Chronobiol Int* 2016; **33:** 351–73.

193 Yatham LN, Vieta E, Goodwin GM, et al. Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *Br J Psychiatry* 2016; **208:** 78–86.

194 Prieto DI, Zehgeer AA, Connor DF. Use of suvorexant for sleep regulation in an adolescent with early-onset bipolar disorder. *J Child Adolesc Psychopharmacol* 2019; **29:** 395.

195 Shariq AS, Rosenblat JD, Alageel A, et al. Evaluating the role of orexins in the pathophysiology and treatment of depression: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92:** 1–7.

196 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:** 31–39.

197 Mischoulon D, Zajecka J, Freeman MP, Fava M. Does folic acid interfere with lamotrigine? *Lancet Psychiatry* 2016; **3:** 704–05.