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ORIGINAL ARTICLE

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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

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The Canadian Network for Mood and Anxiety Treatments (CANMAT) previously published treatment guidelines for bipolar disorder in 2005, along with international commentaries and subsequent updates in 2007, 2009, and 2013. The last two updates were published in collaboration with the International Society for Bipolar Disorders (ISBD). These 2018 CANMAT and ISBD Bipolar Treatment Guidelines represent the significant advances in the field since the last full edition was published in 2005, including updates to diagnosis and management as well as new research into pharmacological and psychological treatments. These advances have been translated into clear and easy to use recommendations for first, second, and third- line treatments, with consideration given to levels of evidence for efficacy, clinical support based on experience, and consensus ratings of safety, tolerability, and treatment-emergent switch risk. New to these guidelines, hierarchical rankings were created for first and second- line treatments recommended for acute mania, acute depression, and maintenance treatment in bipolar I disorder. Created by considering the impact of each treatment across all phases of illness, this hierarchy will further assist clinicians in making evidence-based treatment decisions. Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine alone or in combination are recommended as first-line treatments for acute mania. First-line options for bipolar I depression include quetiapine, lurasidone plus lithium or divalproex, lithium, lamotrigine, lurasidone, or adjunctive lamotrigine. While medications that have been shown to be effective for the acute phase should generally be continued for the maintenance phase in bipolar I disorder, there are some exceptions (such as with antidepressants); and available data suggest that lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination treatments should be considered first-line for those initiating or switching treatment during the maintenance phase. In addition to addressing issues in bipolar I disorder, these guidelines also provide an overview of, and recommendations for, clinical management of bipolar II disorder, as well as advice on specific populations, such as women at various stages of the reproductive cycle, children and adolescents, and older adults. There are also discussions on the impact of specific psychiatric and medical comorbidities such as substance use, anxiety, and metabolic disorders. Finally, an overview of issues related to safety and monitoring is provided. The CANMAT and ISBD groups hope that these guidelines become a valuable tool for practitioners across the globe.

1 | INTRODUCTION

In the 20 years since the Canadian Network for Mood and Anxiety Treatments (CANMAT) first published guidelines on the management of BD (BD),[1] there has been an explosion of research on treatment of this illness. During this time period, CANMAT has strived to translate advances in research into international consensus on evidence-based clinical management; first by publishing 2005 guidelines accompanied by expert commentaries, then by providing updates in 2007,[2] 2009[3] and 2013[4] in collaboration with the International Society for Bipolar Disorders (ISBD). The main objective of these publications was to synthesize the wealth of evidence on the efficacy, safety, and tolerability of the range of interventions available for this complex and varied illness, with the goal of providing clear, easy to use recommendations for clinicians to improve outcomes in their patients.

Given that 13 years have elapsed since the publication of the last full edition in 2005, the objective of these 2018 CANMAT and ISBD Bipolar Disorder Management Guidelines is to provide a comprehensive, up-to-date review of research evidence on the treatment of various phases of BD, translated into clinical recommendations for evidence-based management. Updated principles related to diagnosis and management are also included, in response to significant changes made in the 5th edition of the American Psychiatric Association Diagnostic and Statistical Manual for Mental Disorders

(DSM-5).[5] With increased research into various treatments for BD, the evidence ratings have also been modified to increase rigor; for instance, minimum sample sizes are now specified for randomized controlled trials (RCTs) at each level of evidence (Table 1).

As with previous editions of CANMAT guidelines, clinical support for efficacy was an important consideration in arriving at the final treatment recommendations (Table 2). Major conflicting data are addressed in blue text boxes (figures) to clarify the rationale for arriving at a specific level of evidence for efficacy.

In the current edition, an additional distinction is made between safety and tolerability, and a consensus rating is assigned to each medication on these two measures when used in both the acute and maintenance phase. Further, a rating is also assigned to each medication for its propensity to switch patients into mania or depression (treatment-emergent switch). More information on these ratings can be found in the respective treatment sections, as well as in Section 8.

The final grading of recommendations into first, second, or third-line considers levels of evidence for efficacy, clinical support based on experience, and consensus ratings of safety, tolerability, and risk of treatment-emergent switch. In addition, hierarchical rankings were created and are listed in the tables for first and second line recommendations for acute mania, depression and maintenance treatment in bipolar I disorder (BDI). This hierarchy was created by considering the impact of each treatment across all phases of illness (Figure 1). The rationale for the hierarchical approach is that BD is a chronic lifetime condition with recurrent mood episodes and subsyndromal mood symptoms, and most if not all patients will require maintenance treatment. Since treatments that are prescribed for an acute mood episode are usually continued into maintenance treatment, maintenance efficacy should be considered when choosing acute-phase treatments. Treatments that have demonstrated efficacy across the spectrum of the illness should thus be tried first before treatments that have demonstrated efficacy for only selective phases of the disorder. As an example, if two treatments are shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, the treatment with evidence for maintenance would be placed higher in the hierarchical ranking.

Of note, when a treatment is listed as a monotherapy, that implies that it may be used on its own or in combination with other ongoing treatments, even if there are no specific studies demonstrating the efficacy of that combination. In this situation, the assumption is that the previous ongoing treatment was partially effective, and the addition of the new agent will provide benefits in either an additive or synergistic manner. In contrast, agents specifically listed as adjunctive therapy may have no evidence for efficacy as monotherapy, and/or may have safety concerns if prescribed as monotherapy (eg. antidepressants), and are only recommended for use in combination with other evidence-based agents.

As with previous editions, these guidelines also have a "not recommended" category which includes treatments that have clearly been shown to be ineffective in double-blind RCTs. Further, we have included another category called "no specific recommendation/agents that require further study" to list treatments with insufficient evidence or clinical experience to make a recommendation, or where there is a reason to believe that negative trials failed because of methodological problems-especially when the results are inconsistent with what is expected based on the pharmacological properties of treatment and clinical experience. Inclusion in this category means the efficacy of these agents is unknown at this time.

As in previous editions, these guidelines are organized into eight sections (Table 3), including the Introduction. Foundations of management (Section 2) discusses the epidemiology of BD, screening and diagnostic considerations, the importance of monitoring risk for suicide, the chronic disease management model and patient-centred care (including shared decision making), as well the importance of incorporating psychoeducation and other psychosocial treatment

TABLE 2 Definitions for line of treatment ratings

Line	Evidence level
First	Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch[a]
Second	Level 3 or higher evidence for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch[a]
Third	Level 4 evidence or higher for efficacy plus clinical support for safety/tolerability
Not recommended	Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

[a]The text will specifically note when lack of clinical support for safety/tolerability or risk of treatment-emergent switch has impacted recommendations.

TABLE 1 Definitions for level of evidence ratings

Level	Evidence
1	Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison (n ≥ 30 in each active treatment arm)
2	Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition (n ≥ 30 in each active treatment arm)
3	At least one DB RCT with placebo or active control comparison condition (n = 10-29 in each active treatment arm) or health system administrative data
4	Uncontrolled trial, anecdotal reports, or expert opinion

What are hierarchical rankings?

Hierarchical rankings of treatment options are new to the 2018 Guidelines. They were created for first and second line treatment recommendations for acute mania, depression, and maintenance treatment of bipolar I disorder; and will further assist clinicians in making evidence based treatment decisions.

These orders were created by considering the efficacy of each treatment across all phases, as well as acute and maintenance safety and tolerability and the risk for treatment emergent switch. Thus, for example if two treatments were shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, or had better safety or tolerability, that treatment would be placed higher in the hierarchical recommendation.

When making treatment decisions, we recommend that agents listed higher in the hierarchy be tried first, unless there are patient-specific reasons for choosing an agent lower in the order (such as patient preference, prior treatment non/response, or clinical features which favor treatments lower in the ranking).

FIGURE 1 Hierarchical rankings of treatment recommendations: How were they arrived at? [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Sections

Section 1: Introduction
Section 2: Foundations of management
Section 3: Acute management of bipolar mania
Section 4: Acute management of bipolar I depression
Section 5: Maintenance therapy for bipolar I disorder
Section 6: Bipolar II disorder
Section 7: Specific populations
Section 8: Safety and monitoring

strategies into treatment. Additional information on presentation and hierarchical rankings of treatment options for acute mania (Section 3) and depression (Section 4) are reviewed, and include descriptions of clinical features that may help direct treatment choices. The importance of long-term maintenance treatment and promotion of treatment adherence for mood stability, as well as hierarchical rankings of treatment options are discussed in Section 5. An expert review of the available evidence for treatments of bipolar II disorder (BDII) and recommendations based on those findings are presented in Section 6. The management issues related to specific populations, including women at various stages of the reproductive cycle, children and adolescents, older adults, and those with psychiatric or medical comorbidity are each discussed in Section 7. Finally, the principles of medical monitoring and an overview of safety and tolerability concerns for recommended treatments are provided in Section 8.

For convenience and to avoid confusion, these guidelines also include a table of commonly used terms (with an explanation of the intended meaning) that may have overlapping definitions or criteria in the literature (Table 4).

These guidelines are intended for use by psychiatrists and primary care providers who care for patients with BD throughout the lifespan, supporting them to provide evidence-based assessment, treatment of acute symptoms, prevention of episode recurrence, and management of comorbidities. These guidelines are not meant to replace clinical judgement or define standards of care. While designed with Canadian physicians in mind, input from experts from the ISBD makes these guidelines applicable for practitioners from across the globe. As with previous publications, CANMAT will strive to publish regular updates to these guidelines, incorporating new knowledge useful for practising clinicians.

As not all medications included in these guidelines will be available in all countries, including Canada, clinicians are advised to follow the recommendations of local regulatory bodies.

2 | FOUNDATIONS OF MANAGEMENT

2.1 | Epidemiology

2.1.1 | Prevalence

Bipolar disorder is a common and disabling mental illness with significant morbidity and mortality. The estimates of prevalence of BD vary. The World Mental Health Survey Initiative reported total lifetime (and 12-month) prevalence estimates of 2.4% (1.5%) across BDI, BDII and subthreshold BD subtypes. While the prevalence rates for each subtype varied across the nine countries studied, subthreshold BD was the most common at 1.4% (0.8%), followed by BDI at 0.6% (0.4%) and BDII at 0.4% (0.3%).[6] While Canada was not included in this study, similar results were reported from the Canadian Community Health Survey-Mental Health, which found the lifetime prevalence of BDI was 0.87% and that of BDII was 0.67%.[7]

2.1.2 | Age of onset

Bipolar disorder frequently manifests in late adolescence and young adulthood, with an overall average age of onset of 25 years. Statistical models suggest the presence of three age of onset subgroups within BDI and these can be categorized into a large early-onset group (mean ± standard deviation (SD) 17.24 ± 3.20 years), and smaller middle-onset (23.93 ± 5.12 years) and late-onset (32.20 ± 11.96 years) groups, with the proportion of individuals falling into each category being 41.7%, 24.7% and 33.6% of the total sample, respectively.[8] However, the ages of onset tend to differ somewhat depending upon the origins of samples analysed. For instance, a recent study showed that the

TABLE 4 Clarifying overlapping terminology

Term	Use
Mood stabilizer	Use in the literature is inconsistent, and so this term will not be used in these guidelines
Divalproex	Encompasses valproate, valpromide, valproic acid and divalproex sodium
Conventional antipsychotics	Include first-generation antipsychotics with high affinity for dopamine D2 receptors. Note these are referred to as dopamine receptor antagonists (D2) in the new neuroscience-based nomenclature
Atypical antipsychotics	Comprise second-generation antipsychotics with affinity for dopamine D2 and serotonin 5-HT2 receptors as well as those that have partial agonist effects at D2/D3 receptors. Note these are referred to as dopamine and serotonin receptor antagonists (D2 and 5-HT2A), dopamine 2 partial agonists and serotonin receptor antagonists, and dopamine 2/3 partial agonists in the new neuroscience-based nomenclature
Recurrence	Re-emerging episode(s) of mania or depression whether it be within the previous episode or a new episode. Note that, while the literature may use "relapse" and "recurrence", respectively, inconsistencies in how they are applied and their irrelevance to treatment decisions mean we will use "recurrence" to refer to both
Maintenance	Prophylactic therapy after stabilization of acute manic or depressive episodes

mean age of onset for a USA sample was 20 years, with ages of onset of 14.5 ± 4.9 years (63%), 26.5 ± 7.6 years (28.5%), and 39.5 ± 12.5 years (8.5%) for early-, middle- and late-onset groups, respectively; while a European sample showed a later mean age of onset of 29 years and a later onset in each of the three categories, with 19 ± 2.7 years (24.8%), 27.2 ± 6.3 years (50.7%), and 41.8 ± 10.7 years (24.5%) as the ages of onset for early, middle and late-onset groups, respectively.[9] Those with an earlier age of onset tend to have a longer delay to treatment, greater depressive symptom severity, and higher levels of comorbid anxiety and substance use.[10] While manic episodes can occur for the first time after the age of 50 years as a part of BDI, the possibility of organic mania should be considered and investigated in these cases.[11]

2.1.3 | Burden of illness

People living with BD experience substantial impairment, being symptomatic with syndromal or subsyndromal symptoms, particularly those of depression, for approximately half of their lives.[12,13] Patients are unable to maintain proper work role function approximately 30% or more of the time.[14] Quality of life is reduced in both symptomatic and non-symptomatic patients when compared to healthy controls,[15-17] and several domains of functioning have been identified by patients as being of particular importance- including physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, and education.[18] For both psychosocial functioning and quality of life, impairments are more pronounced in patients with depressive symptoms,[19-21] in those with more previous episodes/longer duration of illness,[20,22] and in those with lower cognition.[23]

Consistent with these observations, the Global Burden of Disease Study attributed 9.9 million years lost to disability (YLD) to BD, making it the 16th leading cause of YLD worldwide.[24] The impact that BD has on young people is even greater, with being the sixth leading cause of disability-adjusted life years among people aged 10-24 years worldwide.[25] The burden of this disease was further emphasized in a systematic review addressing cost of illness studies, with findings demonstrating that the worldwide annual costs per person with BD range from US $1904 to $33 090; higher per person costs associated with BDI, delayed or misdiagnosis, frequent psychiatric interventions, use of atypical antipsychotics, treatment non-adherence, poor prognosis, relapse, and comorbidity.[26]

2.2 | Diagnostic assessment

2.2.1 | DSM-5 diagnostic criteria

Bipolar disorder encompasses a spectrum of diagnostic subgroups primarily divided according to the severity of mood elevation experienced during acute episodes[5] On this spectrum, BDI is placed at one pole due to the presence of threshold manic episodes in which features include inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risky behaviour that leads to significant functional impairment, and may include psychotic features, and/or necessitate hospitalization. At the other end of the spectrum, cyclothymia is characterized by subthreshold presentation of hypomanic and depressive symptoms that, while chronic, do not meet diagnostic criteria for a major depressive episode or manic/hypomanic episode. BDII sits between the two conditions with hypomanic episodes qualitatively like manic periods but, although distinct and observable, are not of a sufficient duration or severity to cause significant functional impairment, hospitalization, or psychosis. Individuals with BDII also experience threshold depressive episodes.

DSM-5 has replaced the BD not otherwise specified (NOS) category in DSM-IV with two new categories; other specified bipolar and related disorder and unspecified bipolar and related disorder. Also, DSM-5 includes substance/medication-induced bipolar and related disorder and bipolar and related disorder due to another medical condition. For more detailed discussion of diagnostic categories, the reader is advised to consult DSM-5 and recent Royal Australian and New Zealand College of Psychiatrists guidelines for treatment of mood disorders.[27]

2.2.2 | DSM-5 specifiers for bipolar and related disorders

DSM-5 also includes a range of specifiers that clinicians may use to further clarify the specific course, severity, and features of BDs. While a more detailed description can be found in the DSM-5 manual, the available specifiers and their use across the spectrum are listed in Table 5. Many of these specifiers may also be used to guide treatment decisions for acute mania (Section 3) and depression (Section 4). Amongst these, the mixed features specifier, which has replaced mixed episodes, warrants consideration because of the multiple and complex presentations of mixed states it can give rise to. Furthermore, the nascency of this terminology has meant that treatment data are as yet sparse. DSM-5 has added mixed features as a specifier during an episode of major depressive disorder (MDD) as well, which will probably pose some pragmatic diagnostic challenges and management dilemmas for clinicians.

2.2.3 | Staging bipolar disorder

The course of BD is heterogeneous but, on average, the risk of recurrence increases with the number of previous episodes.[28] In addition, data examining the effect of episodes on the course of illness shows that the number of previous episodes is associated with increased duration and symptomatic severity of subsequent episodes. Moreover, the number of episodes is associated with a decreased threshold for developing further episodes and with an increased risk of dementia in the long term.[28] The progressive course of illness in patients with multiple episodes is called clinical progression and the biological basis of clinical progression is defined as neuroprogression.[28,29]

The concepts of clinical progression and neuroprogression have provided the basis for the development of staging systems in BD.[30] Overall, the staging models describe three broad clinical stages: (I) individuals at increased risk for developing BD due to family history as well as certain subsyndromal symptoms predictive of conversion into full-blown BD; (II) patients with fewer episodes and optimal functioning in the interepisodic periods, and (III) patients with recurrent episodes as well as decline in functioning and cognition.[31] So far, the heterogeneity intrinsic to BD has prevented the clinical use of staging systems.[32] In addition, the field of staging is in its infancy and the ability of staging systems to guide prognosis and treatment is still to be determined. Overall, the model of staging has helped clinicians to appreciate the importance of early identification and treatment as well as illness trajectories in BD.[33]

2.2.4 | Screening and diagnosis of bipolar disorder

Due to frequent depressive onset, variable help seeking for hypomanic or manic periods, temporal instability of symptoms, and high rates of comorbidity; accurate the timely identification of BD can be difficult to achieve in many cases. Indeed, many individuals are not accurately diagnosed until up to 10 years after the onset of symptoms, with one to four alternate diagnoses typically being given prior to correct recognition and treatment[34,35] This delay has important consequences, including inadequate initial treatment and worse prognosis in terms of episode recurrence and functional outcome.[36,37]

The most frequent misdiagnosis is that of MDD, as patients are more likely to present for the treatment of depressive symptoms and may not recall periods of hypomania or mania, or may not interpret them as being pathological. Recall and insight are particularly impaired during periods of acute depression, with pronounced memory or concentration difficulties. There are several features of depression that may increase suspicion of bipolarity, and prompt more careful investigation, including earlier age of illness onset, highly recurrent depressive episodes, a family history of BD, depression with psychotic features, psychomotor agitation, atypical depressive symptoms such as hypersomnia, hyperphagia, and leaden paralysis, postpartum depression and psychosis, past suicide attempts, and antidepressant-induced manic symptoms or rapid cycling (Table 6) Given the recent change in DSM-5 to allow the possibility of depression symptoms with subthreshold simultaneous hypomanic symptoms (mixed specifier), it is also important to explore if an individual is experiencing mixed symptoms.[38,39] Schizophrenia and other psychotic disorders are the second most

TABLE 5 DSM-5 specifiers for bipolar and related disorders

Specifier	Manic episode	Depressive episode	Illness course
Anxious distress	X	X	
Mixed features	X	X	
Rapid cycling			X
Melancholic features		X	
Atypical features		X	
Psychotic features	X	X	
Catatonia	X	X	
Peripartum onset	X	X	
Seasonal pattern			X
Remission	X	X	
Current episode severity	X	X	

common misdiagnosis, occurring as the initial diagnosis in as many as 30% of patients.[40]

In addition to this under-diagnosis, there are also concerns that BD may be over-diagnosed in some circumstances.[41] For instance, the symptoms of borderline personality disorder, substance use disorder (SUD) and attention deficit hyperactivity disorder (ADHD) overlap significantly those of hypomania/mania, and some reports suggest that patients with these conditions often get misdiagnosed with BD. These conditions also are often comorbid with BD, which makes the diagnosis of this condition often challenging.[42]

Validated self-report instruments, such as the Mood Disorders Questionnaire (MDQ), may be used as a screening tool to flag patients for whom a more detailed assessment is needed. It is important to note, that such tools have poor sensitivity and specificity, especially in community or highly comorbid populations, and will thus have an elevated risk of also flagging those with borderline traits.[43] As such, tools such as the MDQ should be used only as an adjunct for screening clinical populations and not for diagnostic or treatment planning purposes.

To improve the accuracy of diagnosis, it is important that clinicians strictly adhere to diagnostic criteria rather than relying on heuristics.[44] It is important to complete a careful psychiatric history, including in first-degree relatives, with attention paid to any suspected periods of increased activity, irritability, or other change in behaviours. Collateral information from friends and family members should be included wherever possible. Ongoing monitoring of symptoms, such as mood charting, can also help to detect bipolarity that may only become apparent over time. Confirmation of the diagnosis can then be made more confidently when episodes are prospectively observed.

2.2.5 | Comorbidities and mimics

As described in Section 6, patients diagnosed with BD very commonly have one or more comorbid psychiatric diagnoses, with SUDs, impulse control disorders, anxiety disorders, and personality disorders (especially cluster B disorders) particularly common.[45] The presence of comorbidity increases the complexity of the illness and can make an accurate diagnosis even more difficult.

In addition to differentiating BD from other psychiatric diagnoses, alternative causes of mood symptoms, such as personality disorders, medical or neurological conditions, substance use, and medications must be considered in the differential diagnosis (Table 7).

2.3 | Suicide risk

It is important for clinicians to frequently monitor suicidal ideation and risk. Suicide is one of the leading causes of death in BD, with approximately 6%-7% of identified patients with BD dying by suicide; thus, suicide risk is substantially higher in BD than in the general population (10.7 per 100 000 per year).[46,47] The fatality of suicide attempts is also higher in BD than in the general population.[48,49] Worldwide, approximately 43% of patients with BD report suicidal ideation, 21% a plan, and 16% a suicide attempt within the past year.[6] Men are at a higher risk of death by suicide, with an estimated rate of 0.366 per 100 person years, compared to 0.217 for women.[47]

As reviewed in the ISBD Task Force on Suicide in Bipolar Disorder,[50] a number of sociodemographic and clinical risk factors need to be considered in determining the level of suicide risk (Table 8). Factors reported to be significantly associated with suicidal attempt include female sex, younger age of illness onset, depressive polarity of first illness episode, depressive polarity of current or more recent episode, comorbid anxiety disorder, comorbid SUD, comorbid cluster B/borderline personality disorder, first-degree family history of suicide, and previous suicide attempts. Only male sex and first-degree family history of suicide have been significantly associated with suicide deaths.[50,51] The periods during and following hospital admission further represent times of particularly high risk, with 14% of suicides occurring during an inpatient stay and another 26% within 6 weeks of discharge.[47,52]

A comprehensive assessment for suicide risk should occur during all clinical interactions. Risk stratification using assessment tools is not sufficiently accurate for prediction of suicide risk in clinical use; instead, clinical assessment should focus on modifiable risk factors that could be targeted to reduce the risk.[53] The ISBD has developed clinical tips and patient information sheets (translated into several languages) that can be useful tools for clinicians, patients and families to develop a comprehensive approach to suicide prevention (http://www.isbd.org/Files/Admin/Knowledge-Center-Documents/Suicide-Prevention-Tip-Sheet.pdf).

TABLE 6 Features of depression that may increase suspicion of a bipolar vs unipolar illness

Feature	Suggestive of bipolarity	Suggestive of unipolarity
Symptomatology and mental state signs	Hypersomnia and/or increased daytime napping Hyperphagia and/or increased weight Other "atypical" depressive symptoms such as leaden paralysis Psychomotor retardation Psychotic features and/or pathological guilt Lability of mood; irritability; psychomotor agitation; racing thoughts	Initial insomnia/reduced sleep Appetite and/or weight loss Normal or increased activity levels Somatic complaints
Course of illness	Early onset of first depression (<25 years) Multiple prior episodes (≥5 episodes)	Late onset of first depression (>25 years) Long duration of current episode (>6 months)
Family history	Positive family history of bipolar disorder	Negative family history of bipolar disorder

Adapted from Mitchell et al.[38] and Schaffer et al.[39]

TABLE 7 Differential diagnosis of bipolar disorder

Diagnosis	Distinguishing features
Major depressive disorder or persistent depressive disorder	Manic or hypomanic episodes probed for and not present
Bipolar or related disorder due to another medical condition	Episodes are judged to be a consequence of a medical condition such as traumatic brain injury, brain tumours such as frontal lobe meningiomas, multiple sclerosis, stroke, Cushing's disease or hyperthyroidism. Onset or exacerbation of mood coincides with that of the medical condition
Substance- or medication-induced mood disorder	Episodes are judged to be a consequence of a substance such as an illicit drug, or a medication (stimulants, steroids, L-dopa or antidepressants) or toxin exposure. Episodes may be related to intoxication or withdrawal
Cyclothymic disorder	Hypomanic symptoms do not meet the full criteria for a hypomanic episode, and depressive symptoms do not meet the criteria for a major depressive episode
Psychotic disorders (schizoaffective disorder, schizophrenia and delusional disorder)	Periods of psychotic symptoms in the absence of prominent mood symptoms. Consider onset, accompanying symptoms, pervious course and family history
Borderline personality disorder[a]	Instability of interpersonal relationships, self-image and mood, with marked impulsivity and a central theme of intense abandonment fears. Early onset and long-standing course. True euphoria and prolonged well-functioning intervals are extremely rare
Narcissistic personality disorder[a]	Grandiosity, need for admiration and lack of empathy of early onset. Grandiosity not associated with mood changes or functional impairments
Antisocial personality disorder[a]	Early onset of disregard for, and violation of, the rights of others, which does not occur only in the context of a manic episode

Adapted from Yatham et al. 2005[2]
[a]Can occur comorbidly with bipolar disorder.

The association between various treatments and suicide risk has been reviewed by the ISBD Task Force and others, which suggest that lithium[54] and, to a lesser extent, anticonvulsants may contribute to preventing suicide attempts and deaths; although more data are needed to determine their relative efficacies. There were limited data on both antipsychotics and antidepressant agents.[47] As the most common method of suicide in this population is self-poisoning, the potential benefits of various treatments should be considered against their risk of toxicity and lethality. One small Canadian study indicated higher rates of lethal doses of antipsychotics (32%), opioids (29%), benzodiazepines (27%), carbamazepine (21%) and diphenhydramine (15%) compared to lithium (3%) in 34 self-poisoning deaths.[55]

2.4 | Chronic disease management

Due to the chronic, relapsing and remitting nature of BD, a long-term, multidisciplinary approach to management is needed. The Chronic Disease Management Model[56] outlines several important principles to enhance long-term care for these individuals and their families (Table 9). After basic clinical management, including attention to diagnosis, comorbidity, and medical health has been established, patient health education and pharmacotherapy should be the initial and foundational steps for all patients. Ideally, the patient will be connected to a health care team which includes at least one other health care professional (typically a nurse) in addition to the psychiatrist for psychoeducation, ongoing monitoring, psychosocial support, and referral to community resources.[57] All patients should have access to a primary care provider to attend to mental and physical health needs. If the patient is stable and discharged to primary care, the mental health care system should provide support directly to the primary care provider with attention to continuity of care.[58] Additional psychosocial treatments (described below) may also be selected to fit the specific needs and preferences of the patient.

A strong therapeutic alliance is central to improve treatment adherence and outcomes.[59,60] Providers should encourage individuals to actively participate in treatment planning, using a shared decision-making approach.[61,62] Whenever possible, family members or key friends should be included as part of the care team. There is evidence that specialized, team-approach-based interventions combining pharmacotherapy and psychoeducation are more effective than standard community care.[63]

Regular, ongoing monitoring of mood symptoms and other measures related to the patient's own individual recovery, such as sleep, cognition, functioning, and quality of life is encouraged.[18] For many patients, daily recording of mood symptoms such as through a mood diary or National Institute of Mental Health (NIMH) Life Chart Method-Self Rating Scale can help identify early warning signs of relapse, as well as outline relationships between mood and treatment or lifestyle factors such as diet, exercise, or stress.[64] While many patients will agree with the value of completing a mood diary, and this strategy has been shown to improve treatment, regular completion can be a burden.[65] Online solutions such as mobile apps may improve adherence,[66] such as the Self-Monitoring and Psychoeducation In Bipolar Patients smartphone app (SIMPLE) which provides weekly and daily mood tests, with reminders to take medication or see their doctor.[67-69]

2.5 | Dealing with stigma

Stigma is an important issue that will impact individuals with BD, as well as their family members, potentially preventing individuals from seeking

TABLE 8 Summary of main factors associated with suicide attempt and suicide deaths in bipolar disorder (BD)

Variable	Increased likelihood of suicide attempts	Increased likelihood of suicide deaths
Sex	Female	Male
Age	Younger Older—higher lethality	Older—higher ratio of deaths/attempts
Race	Minorities—youth only	
Marital status	Single, divorced, single parents	
Age of onset	Younger	
First episode polarity	Depression Mixed symptoms Mania—more violent attempts	
Predominant polarity	Depressive	
Current episode polarity	Depressive Mixed	Depressive Mixed Manic with psychotic features
Other episode characteristics	Mixed features Greater number/severity of episodes Rapid cycling Anxiety Atypical features Suicidal ideation	Hopelessness Psychomotor agitation
Psychiatric comorbidity	Substance use disorder Cigarette smoking Coffee intake Anxiety disorder Eating disorder	Anxiety disorder
Personality disorders	Present—particularly borderline or cluster B	
Physical comorbidity	Obesity or high BMI	
First-degree family history	Mood disorders BD Suicide	Mood disorders BD Suicide
Prior suicide attempts	Present	Present
Early life trauma	Childhood abuse Early life stress	
Psychosocial precipitants	Interpersonal problems Occupational problems Bereavement Social isolation	Present within 1 week of death
Sexual dysfunction	Present	

Adapted from Schaffer et al.[50]
BMI, body mass index.

or engaging in treatment or causing them to conceal their illness, reducing social support, functioning and quality of life.[70] Linked to stereotypical negative attitudes that mental illness is due to personal weaknesses or decisions, or associated with violent or criminal behaviour, stigma can be perceived or experienced with interactions with others, including health care providers, or internalized (self-stigma). Specific strategies to reduce stigma, particularly self-stigma, by enhancing coping skills through improvements in self-esteem, empowerment, and help-seeking behaviour can improve outcomes in this population.[71]

2.6 | Psychosocial interventions

While pharmacotherapy is essential and forms the foundation for the successful treatment of BD, adjunctive psychosocial interventions may also be useful for acute depressive episodes, as well as in maintenance treatment to prevent relapse and to restore quality of life to the individual and family.[72,73] No evidence exists, and hence there are no recommendations, for specific psychosocial interventions in acute mania. Positive evidence has been found for psychoeducation, cognitive behavioural therapy (CBT), family-focused therapy (FFT), interpersonal and social-rhythm therapy (IPSRT), and peer support in the maintenance phase of BD and these interventions are included as recommended adjunctive treatment options. Additional studies are needed before conclusions can be drawn regarding other strategies such as family/caregiver interventions, dialectical behavioural therapy (DBT), mindfulness-based cognitive therapy (MBCT), cognitive and functional remediation, and online interventions (Table 10).

In general, provision of psychoeducation to all patients and family members is recommended for prevention of relapse, particularly at illness onset, with selection of any additional psychosocial therapies based on individual concerns/presentations or deficits.

2.6.1 | Psychoeducation

Psychoeducation broadly includes provision of information about the nature of the illness, its treatments, and key coping strategies to the patient and family.[74] Current psychoeducational models for BD teach skill development in detecting and managing prodromes of depression and mania, ongoing stress management, problem solving, how to diminish the effects of stigma and denial of the illness, and provide tips on enhancing medication adherence and developing healthy lifestyles (eg, minimizing the use of alcohol, tobacco, drugs, stimulants such as caffeine; getting regular exercise; and regulating sleep and wake times). A key goal is the creation of personalized coping strategies to prevent mood relapse.

Psychoeducation may be delivered individually or in group settings. Empirical models of psychoeducation involve face-to-face interaction with a therapist, but new models are being tested that involve online tools, smartphone apps, and workbooks.[75] Consistent with broader theories of learning, it is believed that psychoeducation is enhanced when it features active learning, with attention to monitoring the development of understanding, active skill development, and homework between sessions. Peer support and group learning are also postulated to add efficacy to psychoeducation. Regardless of the type of model and content included, priority should be given to maximize the therapeutic alliance, convey empathy, and consistently monitor symptoms.[76]

TABLE 9 The chronic disease management model

Self-management support	Empower and prepare patients to manage their health and health care
	Use effective self-management support strategies that include assessment, goal setting, action planning, problem solving, and follow-up
Decision support	Promote clinical care that is consistent with scientific evidence and patient preferences
	Embed evidence-based guidelines into daily clinical practice and share this and other information with patients to encourage their participation
	Use proven provider education materials
Community	Encourage patients to participate in effective community programs
	Form partnerships with community organizations
Delivery system design	Provide clinical care and self-management support that patients understand and that fits with their cultural background
	Ensure regular follow-up by the care team, with defined tasks for different team members
	Provide clinical case management services for complex patients
Clinical information systems	Provide timely reminders for providers and patients
	Facilitate individual patient care planning
	Share information with patients and providers to coordinate care
Health system	Measure outcomes and use information to promote effective improvement strategies aimed at comprehensive system change
	Develop agreements that facilitate care coordination within and across organizations

Adapted from Wagner.[56]

Two models of psychoeducation, both delivered in group format to individuals who are well (euthymic), have published manuals and have substantial research support. These programmes, the Barcelona BDs Program[77] (21 sessions over 6 months) and the Life Goals Program[78] (phase I is six weekly sessions), also have tools to aid implementation with workbooks and handout materials, and both are first-line psychoeducational interventions based on level 2 evidence for the prevention of relapse. Individual psychoeducation based on these manuals would probably be effective, and when individual trials utilizing several different approaches to psychoeducation are combined in a meta-analysis, individual psychoeducation of at least five sessions would still be a first-line intervention for relapse prevention, based on level 2 evidence.[75,79,80] One large study demonstrated that the six-session Life Goals Program psychoeducational intervention was equivalent in relapse prevention to 20 sessions of individual CBT, at far lower cost,[81] with probable shared mechanisms.[82] Furthermore, that study demonstrated that integration of best practices in medication and psychotherapy simultaneously produced striking overall improvement in course of illness.[83] Psychoeducation does not have any significant evidence of utility in either acute depressive or manic episodes.

2.6.2 | Cognitive behavioural therapy

CBT in BD is supported by several published manuals and typically is given in 20 individual sessions over 6 months, often with additional booster sessions. Despite evidence of efficacy for CBT for MDD and psychosis, the results of CBT trials for BD have been mixed. One large RCT supports it use for acute bipolar depression[84] in a trial that compared the efficacy of up to 30 (mean 14) CBT sessions against those of FFT, IPSRT, and a three-session control intervention, but it was not possible to identify whether the benefits came from changes in the medications prescribed or the psychosocial treatments. Efficacy of CBT in relapse prevention was observed in one RCT,[85] but not in another larger RCT, at least in patients who had multiple mood episodes.[86] From meta-analyses, effects on either depressive symptoms or on relapse remain uncertain due to important methodological problems and study selection factors.[87-89] A promising new direction in CBT has been established by a pilot study of "recovery-focused CBT" where 33 subjects received the novel CBT intervention, with evidence of reduction of relapse in the intervention group.[90] Group CBT in euthymic patients with BD is also a new direction and has shown to increase time in remission.[91]

In MDD, CBT, interpersonal psychotherapy (IPT) and behavioural activation have been explored in multiple RCTs and in general display similar efficacies.[92] Based on this and the findings of the study by Miklowitz and colleagues in acute bipolar depression,[84] CBT is still recommended as an adjunctive second-line treatment for acute bipolar depression (level 2). The recommendation is also second-line for maintenance treatment (level 2) for patients with fewer episodes and less severe form of illness. No evidence exists, and hence no recommendation is made, for CBT in mania.

TABLE 10 Strength of evidence and recommendations for adjunctive psychological treatments for bipolar disorder[a]

	Maintenance: Recommendation (Level of Evidence)	Depression: Recommendation (Level of Evidence)
Psychoeducation (PE)	First-line (Level 2)	Insufficient evidence
Cognitive behavioural therapy (CBT)	Second-line (Level 2)	Second-line (Level 2)
Family-focused therapy (FFT)	Second-line (Level 2)	Second-line (Level 2)
Interpersonal and social rhythm therapy (IPSRT)	Third-line (Level 2)	Third-line (Level 2)
Peer support	Third-line (Level 2)	Insufficient evidence
Cognitive and functional remediation	Insufficient evidence	Insufficient evidence
Dialectical behavioural therapy (DBT)	Insufficient evidence	Insufficient evidence
Family/caregiver interventions	Insufficient evidence	Insufficient evidence
Mindfulness-based cognitive therapy (MBCT)	Insufficient evidence	Insufficient evidence
Online interventions	Insufficient evidence	Insufficient evidence

[a]See text for specific definitions of type of therapy and number of sessions needed ("dose of psychosocial intervention") corresponding to this recommendation and evidence.

2.6.3 | Family-focused therapy

FFT[93] presumes that outcomes in BD may be enhanced with the support and cooperation of family or significant others, particularly in families characterized by high levels of expressed emotion. FFT focuses on communication styles between patients and their families or marital relationships, with the goal of improving relationship functioning, and is delivered to the family and patient in 21 sessions over 9 months.

For acute bipolar depression in adults, an intensive FFT (up to 30 sessions; mean 14) out-performed a three-session control condition,[94] although this study was limited by the caveats identified for CBT and IPSRT. Given that the original creation of FFT targeted factors related to depression, it may have specific antidepressant activity, which is also suggested by reduced depression relapse in maintenance studies. For relapse prevention, four significant RCTs of varying sizes have been conducted, delivered to a mixed audience of young adults and adolescents.[95] In these studies, FFT demonstrated efficacy in reducing recurrence of new episodes of depression, but not mania. Overall, FFT is recommended as adjunctive second-line treatment for acute depression (level 2) and for maintenance (level 2). No evidence exists, and hence no recommendation is made, for FFT for mania.

2.6.4 | Interpersonal and social rhythm therapy

IPSRT expands on the IPT focus on grief, interpersonal role transition, role dispute, and interpersonal deficits by including regulation of social and sleep rhythms, specifically targeted to the bipolar population. It is typically delivered in 24 individual sessions over 9 months.[96,97]

Few controlled trials of IPSRT have been conducted, with limited evidence of acute efficacy. The first, large trial[98] showed no effect of IPSRT compared to a control condition but did show benefit for reduction of relapse and improved occupational functioning. An acute bipolar depression study[84] showed intensive IPSRT (up to 30 sessions; mean 14) out-performed a three-session control condition, but it is impossible to state whether the performance was related to the intensity and number of sessions, changes in medication use, or specific attributes of IPSRT. Two small studies failed to demonstrate specific benefits of IPSRT compared to control conditions.[99,100] Other open studies have shown some pre-post benefits in very small samples.[101-103] Again, since many psychosocial treatments for bipolar disorder share common core elements that may be psychoeducational, it is possible that the relapse prevention aspects of psychoeducation may also result from IPSRT interventions, mediated by the same therapeutic processes.[104]

Overall, IPSRT is recommended as an adjunctive third-line treatment for acute depression and for maintenance, based on limited (effect size and small sample size) level 2 evidence in each phase. No evidence exists, and hence no recommendation is made, for IPSRT for mania.

2.6.5 | Peer interventions

Peer interventions, such as peer groups or one-on-one support, are an important strategy believed to reduce self-stigma and isolation in BD, and to help improve engagement in treatment.[105] Some caution is needed when applying this strategy, however, as there may be risks if the peers delivering the intervention are not adequately trained or supported, and if they promote a viewpoint that does not support treatment compliance or promotes substance use.

Reviews of peer interventions for persons with serious mental illnesses, usually incorporating a small but significant number of individuals with BD, have demonstrated modest evidence from RCTs and other controlled studies suggesting that there are important improvements in self-efficacy and reduction in self-stigma.[106-109] The largest peer intervention study involving BD allocated 153 individuals to attend 21 weekly group psychoeducation events, with another 151 assigned to attend 21 weekly group peer support events. The two programmes achieved similar outcomes in terms of time to relapse, and increased knowledge about BD, although psychoeducation was more acceptable to the subjects and worked more effectively at preventing relapse in a subset of people with fewer previous episodes.[110]

A significant source of peer support is emerging from online resources, particularly through the websites of peer advocacy organizations such as the Depression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=peer_landing), the Mood Disorders Association of Ontario (https://www.mooddisorders.ca/), the research and advocacy group CREST.BD (http://www.crestbd.ca/), MoodSwings (www.moodswings.net.au/), and Revivre (http:/wwww.Revivre.org). YouTube is also emerging as an important source of peer support, along with other social media.[111,112]

Overall, peer interventions receive a third-line treatment recommendation (level 2) as an adjunctive maintenance therapy.

2.6.6 | Other psychosocial interventions

Various other approaches have been tried in BD, with a variety of aims, modalities, and outcome targets. None of the other interventions have been specifically targeted for bipolar depression or for mania. Some have been designed in part to reduce episode recurrence, but none have been successful in providing substantial evidence of efficacy. Because CANMAT recommendations are for the treatment of acute depression and mania, and maintenance treatment to prevent them, we do not make specific recommendations regarding these treatments. However, some of these approaches have been helpful in ameliorating some important symptoms in individuals with BD, (such as residual mood symptoms or anxiety) and so we will describe them briefly.

Although somewhat like FFT, family/caregiver interventions constitute a distinctly different psychosocial intervention in that the intervention is given to the family/caregiver, not the person with BD, and evidence exists that such interventions improve clinical outcomes in the patient.[75,113] Clinical wisdom and common practice, however, support the importance of family or caregivers being included in at least some sessions with the patient (particularly for psychoeducation), both to reduce symptom burden on the individual with BD and to reduce burnout and emotional burden on the caregiver. Validated caregiver resources are available online, such as www.bipolarcaregivers.org.[114]

DBT, which includes distress tolerance training, has several small studies showing its utility in the reduction of some depressive symptoms and suicidality.[75]

One RCT of MBCT involving 95 patients did not demonstrate any difference in relapse prevention compared to a treatment-as-usual group, but did reveal fewer anxiety and depressive symptoms in the MBCT arm.[115] Coupled with the findings of other smaller studies, this suggests that MBCT may have a role to play in anxiety reduction in BD.[75,116]

While not reviewed here, given that individuals with BD may have histories of childhood abuse and comorbid personality disorders, and experience various sequelae such as shame or conflict due to behaviours experienced during acute bipolar episodes, all of these may rightly be a target for psychosocial intervention in a very individualized manner.

2.6.7 | Cognitive and functional remediation

Functional impairment as well as cognitive deficits are found in many individuals with BD, not just during an acute episode but even between episodes, prompting the evaluation of various psychosocial and biological strategies to address these problems. One intervention, functional remediation (FR), involves a 21-session group intervention over 6 months. In a large RCT, FR was shown to have a substantial impact on functioning, in comparison to treatment as usual.[117] Coupled with the results of other small studies involving other interventions, these findings suggest that there is considerable hope in addressing cognitive and functional deficits in BD.[118] Computer-based cognitive remediation, though, may show positive effects on cognition but not on functioning.[119]

2.6.8 | Online and digital strategies

Modern trends to rely on the internet and apps, along with access problems in mental health, have led to the study of various online tools and mobile phone apps.[120] Such strategies also build on strong traditions of self-monitoring and self-management developed formally in traditional psychoeducational interventions. In reviews, such internet and mobile health interventions have shown good adherence to validated psychological health principles, good acceptability to patients, ease of access, and ease of use. However, research is mostly limited to pilot studies and the relatively few larger studies have not shown unequivocal benefit.[68,121]

3 | ACUTE MANAGEMENT OF BIPOLAR MANIA

3.1 | Presentations of mania

DSM-5[5] made a change to "criterion A" for mania which now requires a distinct period of abnormally and persistently elevated, expansive, or irritable mood *and* abnormally and persistently increased activity or energy present most of the day, nearly every day for at least 1 week (or less time if hospitalization is necessary). In addition, a diagnosis of a "manic episode" requires at least three (or four if the mood is only irritable) of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure of speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increased goal-directed activity or psychomotor agitation, or excessive involvement in activities with a high potential for painful consequences. The mood disturbance must lead to marked impairment in functioning, require hospitalization, or be accompanied by psychotic features.

Unlike DSM-IV, DSM-5 allows a diagnosis of BDI in patients with major depression whose mania emerges during treatment (eg, during medication or electroconvulsive therapy [ECT]) and persists at a fully syndromal level beyond the physiological effect of the treatment.

DSM-5 has eliminated the categorical "mixed episode" specifier, replacing it with the more dimensional "mixed features". DSM-5 also

includes other specifiers that can accompany a manic episode: anxious distress, rapid cycling, mood-congruent or mood-incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern (Table 5). The utility of several of these specifiers in selecting treatment options for mania is discussed later in this section (see "Clinical features that help direct treatment choice").

3.2 | Management of agitation

Agitation is common in mania, and is particularly frequent in patients who have mixed features.[122] Defined in DSM-5 as "excessive motor activity associated with a feeling of inner tension",[5] agitation can manifest as pacing or fidgeting in mild cases to uncooperative, threatening, or aggressive behaviours in severe cases. Severe symptoms of agitation require prompt attention in order to reduce distress, mitigate potentially dangerous behaviour, and allow for an assessment and evaluation of underlying manic symptoms.[123]

A key step in treating agitation is preventing it, or at least mitigating its severity, by rapidly treating the causative manic episode. When addressing agitation in patients with BDI, clinicians need to be aware that akathisia may present as agitation and, therefore, this must be excluded before implementing the general principles of management of acute mania described in step 1 (see "Pharmacological treatment of manic episodes"). Since agitation in this context is a manifestation of mania, it is assumed that effective interventions for treating mania that have rapid onset of efficacy would be effective in reducing agitation. Therefore, if the patient is agreeable to taking oral medications, antimanic agents with rapid onset of efficacy should be considered first.

When agitation persists despite administration of antimanic treatments, additional rapidly acting pharmacotherapy may often be needed. The evidence for specific efficacy of various agents in short-term treatment of agitation is summarized in Table 11. Some of these agents are either not available or rarely used in North America (eg, midazolam and promethazine). We further note that the dose ranges in Table 11 are based on the doses studied in the trials, and would probably be appropriate in most situations. However, a comprehensive evaluation of the agitated patient is necessary (ie, medical conditions, treatments, drugs, intoxication, etc.) to determine a safe and adequate dose.

As can be seen from Table 11, the highest level of evidence available in short-term treatment of agitation for oral formulations of any agent is level 3, and level 2 for intramuscular (IM) or inhaled formulations. In this context, it is important to remember that the absence of evidence does not constitute lack of efficacy. Indeed, clinical experience suggests that agitation in many patients with acute mania responds well to the oral medications. Thus, a loading dose of divalproex, oral formulations of atypical antipsychotics, conventional antipsychotics such as haloperidol or loxapine, and/or benzodiazepines such as lorazepam may be appropriate. If a patient indicates willingness to take oral treatment but there is a suspicion that the patient might "cheek" the medication, then either orally dispersing tablets (ODT), those that rapidly melt, oral liquid, or oral inhalation forms should be considered. In countries where inhaled loxapine is available, this could be considered if there are no contraindications.

If oral preparations are ineffective or if the agitation is severe and if the patient is refusing oral medications, or when oral therapy cannot be safely or reliably administered, then IM formulations should be considered.[124] Because of the strength of evidence for efficacy in alleviating agitation in this population, aripiprazole IM (level 2),[125,126] lorazepam IM (level 2),[125,127] loxapine inhaled (Level 1)[128,129] and olanzapine IM (level 2)[127,130-133] are recommended as the first-line option. Sublingual asenapine (level 3),[134] haloperidol IM (level 3),[131,135,136] haloperidol IM + midazolam IM (level 3),[131,137] haloperidol IM + promethazine IM (level 3),[131,137,138] risperidone ODT (level 3),[136] and ziprasidone IM (level 3)[131,137,139] are recommended as a second-line treatment. Haloperidol per os (PO) (level 4),[140,141] loxapine IM (level 4) (clinical opinion), quetiapine PO (level 4),[141] and risperidone PO (level 4)[140] are included as third-line options (Table 11).

3.3 | Pharmacological treatment of manic episodes

There are a range of strategies that have been investigated for use in mania; including lithium, divalproex, other anticonvulsants, typical and atypical antipsychotics, and other agents and therapies. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). The evidence for efficacy and the recommendations for treating acute mania are summarized in Table 12.

As stated previously, the first and second-line agents are listed hierarchically taking into consideration not only their efficacy for acute mania but also their efficacy in preventing mania or depression, treating acute bipolar depression, safety/tolerability and the risk of treatment-emergent switch. The implication of this hierarchical recommendation is that those listed higher up in the table should be considered first before moving on to the next on the list, unless other factors such as history of previous non-response or patient's preferences preclude such strategy in a given patient.

Monotherapy and combination therapy are listed separately as first-line treatments for acute mania in Table 12. This does not mean that all monotherapy agents should be tried first before considering combination therapy for acute mania. We suggest that the treating clinician make a decision as to whether to treat a given patient with monotherapy or combination therapy. That decision is typically based on the rapidity of response needed (eg, combination treatments tend to work faster), whether the patient had a previous history of partial response to monotherapy, severity of mania, tolerability concerns with combination therapy, and willingness of the patient to take combination therapy. Once a decision is made whether to treat the patient with monotherapy or combination therapy, then hierarchy related to monotherapy or combination therapy could be followed. We also suggest that clinicians evaluate the efficacy and tolerability at the end of weeks 1 and 2 and modify treatment options accordingly.

TABLE 11 Level of evidence and recommendations for short-term pharmacological management of agitation[a]

Level of recommendation	Agent	Formulation	Level of evidence	Dose range of studies[b]	
				Single dose	Max/24 h
First-line	Aripiprazole	IM	2	9.75 mg	15 mg
	Lorazepam	IM	2	2 mg IM	
	Loxapine	Inhaled	1	5 mg	10 mg
	Olanzapine	IM	2	2.5 mg	10 mg[c]
Second-line	Asenapine	Sublingual	3	10 mg	
	Haloperidol	IM	3	5 mg	15 mg
	Haloperidol + midazolam	IM	3	2.5 mg (haloperidol) + 7.5 mg (midazolam)	5 mg (haloperidol) + 15mg (midazolam)
	Haloperidol + promethazine	IM[e]	3	2.5 mg (haloperidol) + 25 mg (promethazine)	5 mg (haloperidol) + 50 mg (promethazine)
	Risperidone	ODT[e]	3	2 mg	4 mg
	Ziprasidone	IM[e]	3	2 mg	20 mg
Third-line	Haloperidol	PO[d]	4	5 mg	15 mg
	Loxapine	IM	4	N/A	
	Quetiapine	PO[d]	4	Mean (SD) = 486.7 (317.2) mg/day	
	Risperidone	PO[e]	4	2 mg	

[a]See text for recommendations about use of oral antipsychotics and divalproex. IM, intramuscular; ODT, orally disintegrating tablet; PO, per os.
[b]Doses are reported as per studies.
[c]26.3% received two or three 10 mg injections.
[d]Assessed 2 h after the dose.
[e]Doses are not specifically for bipolar disorder but included schizophrenia or other diagnoses.

3.3.1 | Step 1: review general principles and assess medication status

Examination of a patient presenting in a manic state should include an immediate assessment for risk of aggressive behaviour, violence and safety threat to others, suicide risk especially in those with mixed features, degree of insight and the ability to adhere to treatment, comorbidity (including substance use that may be aggravating or contributing to clinical presentation), and availability of a psychosocial support network. A physical examination with laboratory investigations (described in Section 8) should be conducted, but may be deferred for patients who are uncooperative. Results of the overall assessment should be used to establish the most appropriate treatment setting (eg, ambulatory or inpatient).

Before initiating pharmacological treatment for a manic episode, it is imperative to rule out symptoms secondary to drugs of abuse, medications, other treatments, or a general medical or neurological condition (although, even in these cases, symptomatic treatment may be applied on a short-term basis). Steps should be taken to rule out any other factors that may be perpetuating symptoms such as prescribed medication, illicit drug use/abuse or an endocrine disorder. Any patients presenting with mania who have been taking antidepressants should have these medications discontinued. If there is a previous diagnosis of BD, it is appropriate to immediately commence antimanic agents. If this is the first emergence of manic symptoms, clinicians are advised to confirm the diagnosis of BD by monitoring patients for a period of time after antidepressant discontinuation and obtain collateral information to confirm whether symptoms remain and antimanic treatment is necessary. Patients should also be supported to discontinue stimulant use, including caffeine and alcohol. Current and prior therapies should be assessed, including appropriateness of medications, dosing, and trough serum levels (where indicated), as well as past response; and this should be used to direct subsequent therapeutic choices. Attention should be paid to managing withdrawal symptoms that may occur in manic patients with histories of substance abuse.

When the symptoms of mania have remitted, behavioural and educational strategies should be applied to promote ongoing medication adherence, reduce residual symptoms, help identify early signs of relapse, and support functional recovery (see Section 2).

3.3.2 | Step 2: initiate or optimize therapy and check adherence

It is recommended that, for all patients (including those who are untreated as well as those receiving a non-first-line treatment), therapy be initiated with one of the available first-line monotherapy or combination treatments.

First-line monotherapy

Approximately 50% of patients will respond to monotherapy with significant improvement in manic symptoms within 3-4 weeks.[142]

TABLE 12 Hierarchical rankings of first and second-line treatments recommended for management of acute mania

	Level of evidence by phase of treatment					Considerations for treatment selection				
		Maintenance				Acute		Maintenance		
	Acute mania	Prevention of any mood episode	Prevention of mania	Prevention of depression	Acute depression	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of depressive switch
First-line treatments: Monotherapies										
Lithium	●	●	●	●	◔	+	+	++	++	–
Quetiapine	●	●	●	●	●	+	++	++	++	–
Divalproex	●	●	◐	◔	◔	–	+	++[e]	+	–
Asenapine	●	◔	◔	◔	n.d.	–	+	–	+	–
Aripiprazole	●	◔	◔	n.d.[a]	■	–	+	–	+	–
Paliperidone (>6 mg)	●	◔	◔	n.d.[a]	n.d.	–	+	+	++	–
Risperidone	●	◕	◕	n.d.	n.d.	–	+	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
First-line treatments: Combination therapies										
Quetiapine + Li/DVP	●	●	●	●	◕[c]	+	++	+++[e]	++	–
Aripiprazole + Li/DVP	◔	◔	◔	n.d.[b]	◕	+	+	++[e]	++	–
Risperidone + Li/DVP	●	◕	◕	n.d.	◕	+	++	+++[e]	++	–
Asenapine + Li/DVP	◔	◕	◕	n.d.	◕	+	+	++[e]	+	–
Second-line treatments: Combination therapies										
Olanzapine	●	●	●	●	●[d]	+	++	+++	++	–
Carbamazepine	●	◔	◔	◔	◐	++	+	++[e]	++	–
Olanzapine + Li/DVP	●	◕	◕	◕	n.d.	+	++	+++[e]	++	–
Lithium + DVP	◐	◐	◐	n.d.	n.d.	+	++	++	++	–
Ziprasidone	●	◕	◕	n.d.	■	++	++	++	+	–
Haloperidol	●	n.d.	◕	◪	n.d.	+	++	+++	++	++
ECT	◐	◕	◕	◕	◕	+	++	+	++	–

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

●, level 1 evidence; ◔, level 2 evidence; ◐, level 3 evidence; ◕, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◐, level 3 negative evidence; ◕, level 4 negative evidence; n.d., no data; –Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Although monotherapies are listed above combination therapies in the hierarchy, combination therapies may be indicated as the preferred choice in patients with previous history of partial response to monotherapy and in those with psychotic mania or in situations where rapid response is desirable.

[b]Did not separate from placebo in those with index mania; no studies available in index depression.

[c]No controlled trials; however, clinical experience suggests that it is a useful strategy.

[d]Did not separate from placebo on core symptoms of depression.

[e]Divalproex and carbamazepine should be used with caution in women of childbearing age.

[Colour table can be viewed at wileyonlinelibrary.com]

Lithium (level 1), quetiapine (level 1), divalproex (level 1), asenapine (level 1), aripiprazole (level 1), paliperidone (level 1 for doses >6 mg), risperidone (level 1), and cariprazine (level 1) are all recommended as first-line treatment options. Overall, these agents show comparable efficacy (Cohen's *d* 0.32-0.66; small to medium effect size).[143]

Although they have comparable efficacy for treating acute mania, we recommend that the agents listed first in the text and placed higher in Table 12 be tried first, in the order listed, unless there are patient-specific reasons for choosing an agent lower down in the order (see "Clinical features that help direct treatment choices"). For instance, lithium should be considered first for acute mania unless there are specific reasons not to, such as mixed features, comorbid substance use or previous non-response to lithium.

Carbamazepine, olanzapine, ziprasidone and haloperidol also have level 1 evidence for efficacy but they are downgraded to second-line options due to safety/tolerability risks with these agents.

First-line combination therapy

Combination therapy with the atypical antipsychotics quetiapine (level 1), aripiprazole (level 2), risperidone (level 1), or asenapine (level 2) and lithium or divalproex is also recommended as first-line treatment options with greater efficacy than monotherapy with lithium or divalproex alone, especially in those with higher index severity.[144]

In general, combination therapy is preferred to mood stabilizer monotherapy because clinical trials suggest that on average about 20% more patients will respond to combination therapy.[142,145,146] There is also some evidence to suggest the benefit of combination therapy compared to atypical antipsychotic monotherapy, although there are fewer trials. Specifically, lithium plus quetiapine showed superiority to quetiapine alone.[147] While there is also level 1 evidence for olanzapine combination therapy over olanzapine monotherapy, this is downgraded to second-line due to tolerability/safety concerns with olanzapine.

The decision to treat with one or a combination of available first-line agents should be informed by current and prior medication use, with treatment previously shown to be successful in managing symptoms preferred. Safety and tolerability factors for each medication and clinical features predictive of better response (see "Clinical features that help direct treatment choices") should also be considered. In general, combination therapy is associated with more adverse events than monotherapy. Whenever possible, options should be discussed with the patient and/or their caregiver and their preferences considered prior to treatment selection.

If symptoms are not controlled using monotherapy or combination therapy with first-line agents, dosing should be optimized, issues of non-adherence identified and addressed, and consideration given to possible substance use (Section 4) prior to adding or switching therapies (Step 3). Given that almost all antimanic agents separated from placebo within 1 week, some therapeutic response is expected with antimanic agents within 1-2 weeks. If no response is observed within 2 weeks with therapeutic doses of antimanic agents, and other contributing factors for non-response are excluded, then switch or add-on strategies should be considered.

3.3.3 | Step 3: add on or switch therapy (alternate first-line agents)

If therapy with one or a combination of the first-line agents (lithium, divalproex and/or an atypical antipsychotic) at optimal doses is inadequate or not tolerated, the next step is to switch to or add on an alternate first-line agent. An exception is that, despite level 1 evidence for monotherapy with paliperidone and ziprasidone, we do not recommend combination therapy with these agents due to lack of evidence for additional efficacy (see "No specific recommendation/agents that require further study" below). Because there are multiple first-line agents with substantial efficacy data and relative safety and tolerability, the use of second- and third-line agents is only recommended after unsuccessful trials of multiple first-line strategies.

3.3.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

In patients who are inadequately responsive to first-line agents, second-line choices include monotherapy with olanzapine (level 1), carbamazepine (level 1), ziprasidone (level 1), and haloperidol (level 1)[143] or combination therapy with olanzapine plus lithium or divalproex (level 1). While each of these strategies has strong support for their efficacy, as indicated above, safety and tolerability concerns relegate them to second-line options. Although widely used in clinical practice, the combination of lithium and divalproex is also recommended as a second-line choice, as evidence supporting its efficacy is limited to uncontrolled trials (level 3).[148-151]

ECT is also recommended as a second-line option (level 3)[152] and, although the number of controlled trials is limited, there is evidence to suggest that up to 80% of patients will show marked clinical improvements.[153] Brief pulse therapy with two or three treatments per week has been used. Bifrontal electrode placement is preferred over bitemporal as it is associated with faster treatment response and fewer cognitive side effects.[154-156]

When all first-line agents have failed, the hierarchy should be applied to second-line agents as well. Hence, olanzapine, which is highest in the hierarchy amongst second-line agents, should be first choice before moving down the list in Table 12.

3.3.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Agents recommended as third-line options for treatment of acute mania include monotherapy with chlorpromazine (level 2),[157] monotherapy with clonazepam (level 2),[158] monotherapy or adjunctive therapy with clozapine (level 4),[159-162] and monotherapy with tamoxifen (level 2).[143] Tamoxifen is downgraded because of the risk of uterine cancer and the lack of clinical experience despite evidence for efficacy. Combination treatments with carbamazepine or oxcarbazepine (level 3),[163] haloperidol (level 2),[144,164] or tamoxifen (level 2)[165] plus lithium or divalproex are

TABLE 13 Additional agents evaluated for use in acute mania

	Agent	Level of evidence
Third-line	Carbamazepine/oxcarbazepine + Li/DVP	Level 3
	Chlorpromazine	Level 2
	Clonazepam	Level 2
	Clozapine	Level 4
	Haloperidol + Li/DVP	Level 2
	rTMS	Level 3
	Tamoxifen	Level 2
	Tamoxifen + Li/DVP	Level 2
Not recommended	Allopurinol	Level 1 negative
	Eslicarbazepine/licarbazepine	Level 2 negative
	Gabapentin	Level 2 negative
	Lamotrigine	Level 1 negative
	Omega-3 fatty acids	Level 1 negative
	Topiramate	Level 1 negative
	Valnoctamide	Level 2 negative
	Zonisamide	Level 2 negative

DVP, divalproex; Li, lithium; rTMS, repetitive transcranial magnetic stimulation.

also included as third-line. Repetitive transcranial magnetic stimulation (rTMS) in the right prefrontal cortex at 110% motor threshold (level 3)[166] can also be considered in combination with pharmacotherapy.

The third-line agents should only be used if a patient has not responded to adequate trials with all first and second-line agents alone and in combination. Given that the evidence is very limited for third-line agents, it was not possible to list them in any hierarchical order and they are thus listed alphabetically (Table 13).

3.3.6 | Agents not recommended for the treatment of acute mania

Antimanic efficacy has not been demonstrated for allopurinol (level 1 negative),[167] eslicarbazepine/licarbazepine (level 2 negative),[168] gabapentin (Level 2 negative), lamotrigine (level 1 negative),[143] omega-3 fatty acids (level 1 negative),[169] topiramate (level 1 negative),[143] valnoctamide (level 2 negative),[170,171] or zonisamide (level 2 negative)[172] (Table 13).

3.3.7 | No specific recommendation/agents that require further study

Trials with paliperidone (level 2 negative) and ziprasidone (level 2 negative) adjunctive therapy to lithium or divalproex showed lack of efficacy.[144] This is surprising given that all other atypical antipsychotic agents that showed efficacy in monotherapy have also been shown to offer additional benefit when combined with lithium or divalproex. It is likely that methodological problems have contributed to failure in these studies; hence, further studies are needed before specific recommendations can be made about the use of these combinations for mania.

Studies of olanzapine (level 2 negative) [173] or risperidone (level 3 negative)[174] plus carbamazepine have been negative, although this is probably due to enzyme-inducing effects of carbamazepine. While this may be overcome by dosing adjustments, because such interactions are unpredictable and effective doses have not been established, we are unable to provide a specific recommendation.

Nutraceuticals such as branched chain amino acids (level 3),[175] folic acid (level 2),[176] and L-tryptophan (level 3),[177] as well as other experimental agents such as medroxyprogesterone (level 3),[178,179] memantine (level 4),[180] mexiletine (level 4),[181] levetiracetam (level 4)[182] and phenytoin (level 3),[183] have all shown indications of efficacy when used adjunctively with other antimanic agents, as have glasses that block blue light (level 3).[184] Larger controlled trials are needed, however, before a recommendation for their use in mania can be made. While an initial small RCT did not show anti-manic efficacy for verapamil,[185] there is some evidence that it may work as an adjunctive therapy (level 4)[186] or as monotherapy in women (level 4).[187] Larger studies are needed before a conclusion can be made.

3.3.8 | Clinical features that help direct treatment choices

Clinical features, including DSM-5 specifiers, may assist in making treatment choices between first and second-line treatment options.

In general, lithium is preferred over divalproex for individuals who display classical euphoric grandiose mania (elated mood in the absence of depressive symptoms), few prior episodes of illness, a mania-depression-euthymia course,[188-190] and/or those with a family history of BD, especially with a family history of lithium response. Divalproex is equally effective in those with classical and dysphoric mania. Further, divalproex is recommended for those with multiple prior episodes, predominant irritable or dysphoric mood and/or comorbid substance abuse or those with a history of head trauma.[188,191-195] Because of its teratogenic potential, however, caution should be exercised when prescribing divalproex to women of childbearing age. Patients with specific factors such as a history of head trauma, comorbid anxiety and substance abuse, schizoaffective presentations with mood-incongruent delusions, or negative history of bipolar illness in first-degree relatives may respond to carbamazepine.[196]

Combination therapy with lithium or divalproex and an atypical antipsychotic is recommended when a response is needed faster, in patients judged at risk, who have had a previous history of partial acute or prophylactic response to monotherapy or in those with more severe manic episodes.[145]

Anxious distress

Symptoms of anxiety frequently co-occur during a manic episode, and are a predictor of poor outcome; including greater severity of manic symptoms,[197] a longer time to remission,[197,198] and more reported side effects of medication.[198] There have been no studies specifically examining the efficacy of any agents in reducing symptoms of anxiety during a manic episode, although these symptoms do tend to improve concurrently with mood disturbance. Post hoc analyses suggest that

divalproex, quetiapine, and olanzapine may have specific anxiolytic benefits[199] and carbamazepine may be useful as well.[196]

Mixed features

Depressive symptoms co-occur alongside mania in 10%-30% of cases,[200,201] with studies suggesting mixed features are indicative of a more severe and disabling course, as well as a higher rate of suicide.[201,202] Evidence supports the preferential use of atypical antipsychotics and divalproex in these cases, with combination therapy frequently required.[195,203] Atypical antipsychotics such as asenapine, aripiprazole, olanzapine and ziprasidone have been shown to be equally effective in treating manic symptoms in those with classical mania as well as in mixed mania or in manic patients with mixed features.[196,204,205]

Psychotic features (mood congruent or incongruent)

At least half of manic episodes are characterized by the presence of psychosis,[206] and theories suggest that it is a nonspecific feature which improves alongside underlying manic symptoms.[207] While the prognosis for patients experiencing mood-congruent psychotic features may not differ from those with an absence of psychotic symptoms, limited evidence does suggest that those with mood-incongruent features have a more severe illness with poorer long-term prognosis.[207-212] There is no evidence of superiority of any first-line monotherapy treatment in comparison to other monotherapy options in treating patients with psychotic features. Similarly, there is no evidence that any first-line combination therapy of lithium or divalproex plus an atypical antipsychotic is more effective than other first-line combination therapy.[174,193,213,214] However, clinical experience suggests that the combination of lithium or divalproex plus an atypical antipsychotic is more appropriate for manic patients with mood-incongruent psychotic features (ie, other than grandiose delusions). Similarly, in patients where the diagnostic possibility of schizoaffective disorder with manic symptoms is considered, either use of an atypical antipsychotic or combination of an atypical antipsychotic with a mood stabilizer is more appropriate.

Rapid cycling

Rapid cycling, or a course of illness that includes four or more mood episodes a year, affects up to one-third of patients with BDI.[215-218] Hypothyroidism, antidepressant use and substance abuse are often associated with rapid cycling; thus assessing thyroid function and discontinuation of antidepressants, stimulants, and other psychotropic agents that are contributors to cycling are imperative. Consideration should be given to gradually withdrawing substances in order to prevent withdrawal, but this needs to be balanced against the severity of mood cycling and the need for rapid mood stabilization. As there is no evidence for the superiority of any first-line treatment in addressing acute manic symptoms in patients with a rapid cycling course,[219] appropriate pharmacotherapy should be selected primarily based on effectiveness in the maintenance phase, if known (see Section 5). It is likely that combinations of mood-stabilizing drugs may be more often necessary than monotherapies when rapid cycling is present,[220] but triple mood stabilizer therapy has not demonstrated superiority to double mood stabilizer therapy in a single RCT,[221] although methodological weaknesses probably limited interpretability of the findings.

Seasonal pattern

While some individual patients may show a seasonal pattern, Canadian data are mixed as to whether episodes of mania or depression in BD follow a consistent seasonal variation.[222] There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

4 | ACUTE MANAGEMENT OF BIPOLAR DEPRESSION

4.1 | Presentations of bipolar depression

The DSM-5 criteria for bipolar depression are unchanged from DSM-IV. Depression is characterized by a minimum of 2 weeks of depressed mood and/or anhedonia and at least four other symptoms that include changes in sleep, appetite/weight, energy, psychomotor activity, concentration, thought content (guilt and worthlessness), and suicidal intent. For many patients with BD, the depressive polarity is often more pervasive and more debilitating than manic states, with estimates that depressed mood accounts for up to two-thirds of the time spent unwell, even with treatment.[12,223,224] Subsyndromal depressive symptoms, which persist despite treatment, are particularly common and a major source of functional impairment in these patients.[225-229] They should be treated aggressively.

DSM-5 includes several specifiers that may accompany depressive episodes: anxious distress, mixed features, rapid cycling, melancholic features, atypical features, mood-congruent or mood-incongruent psychotic features, peripartum onset, and seasonal pattern (Table 5). The utility of several of these specifiers in selecting treatment options for depression is discussed later in this section (see "Clinical features that help direct treatment choices").

4.2 | Diagnostic and treatment challenges

4.2.1 | Misdiagnosis and delayed diagnosis

Patients with depression occurring in the context of BD are frequently misdiagnosed as having MDD, since the presence of mania or hypomania (particularly mild or moderate episodes which do not require hospitalization) may be challenging to establish retrospectively. This is especially true in the absence of a comprehensive diagnostic interview or collateral information, as patients may often lack basic knowledge of what hypomania/mania is, and/or have limited insight into these symptoms; and thus may not disclose this information unless specifically asked. Alternatively, patients who will ultimately present with hypomanic or manic episodes may only have experienced episodes of depression. Thus, clinicians must be vigilant for a diagnosis of BD, and routinely ask for symptoms of a previous manic/hypomanic episode in every patient presenting

with a major depressive episode. A diagnosis of MDD should be made only after excluding the possibility of BD.

In addition to overt manic/hypomanic symptoms, there are numerous features that increase the likelihood of a diagnosis of BD in depressed individuals. These include earlier age of illness onset (before 25 years), brief, highly recurrent depressive episodes, a family history of BD, depression with psychotic features, atypical features such as reverse vegetative symptoms of hypersomnia and hyperphagia, leaden paralysis, psychomotor agitation, postpartum depression or psychosis, and antidepressant-induced irritability, manic symptoms or rapid cycling[38,39] (Table 6).

Individuals with depression who are at high risk for BD, particularly those with a strong family history of BD, should be closely monitored for emergence of manic or mixed symptoms. Consideration should also be given to applying the BD depression treatment recommendations amongst those at very high risk, rather than risk potential iatrogenic effects of antidepressant monotherapy, although this recommendation is based on clinical experience as there is a lack of sufficient research addressing this issue. As discussed in Section 2, there are also several useful psychosocial interventions, such as individual and family psychoeducation and FFT, that have been shown to have some benefit in this population.

4.2.2 | Suicide risk

Principles related to management of suicidal ideation and risk (see Section 2 and[47]) are of utmost importance during depressive episodes, as >70% of suicide deaths and suicide attempts in patients with BD occur during this phase.[230,231] Depressive episodes with mixed features are a particularly dangerous period associated with even higher short-term risks of suicide attempts or death.[232] Overall, it is imperative for clinicians to review risk factors (Table 9) and determine an appropriate treatment setting to address any safety issues. All patients at risk should be encouraged to develop and share a written safety plan listing coping strategies and sources of support which may be applied during times of crisis. As described in Section 2, the most common method of suicide in this population is self-poisoning, and so potential benefits of various treatments should be considered against their risk of toxicity and lethality. One study found that there were fewer deaths due to lethal lithium levels compared to carbamazepine, and that opioids and benzodiazepines were the most common medication classes ingested at lethal levels—noteworthy given the lack of efficacy of these agents in the disorder.[55]

4.2.3 | Cognitive and functional impairment

Part of the impact of acute and subsyndromal depressive symptoms on functional impairment is thought to be mediated through cognitive performance, which is both subjectively and objectively impaired in bipolar depression and linked to poor psychosocial function.[233-236]

Because of the important link between cognition and functioning,[237] attention should be paid to avoiding treatments that may further exacerbate cognitive difficulties[238] (see Section 8). Although evidence for their efficacy is limited, cognitive enhancement therapies can be considered experimental in this population.[72,239,240]

4.3 | Psychological interventions for acute bipolar I depression

While pharmacotherapy is essential and forms the foundation for successful treatment of BD, adjunctive psychosocial interventions may also be useful for acute depressive episodes. As described in Section 2, there are no first-line psychosocial treatment options for acute bipolar depression. Selecting between second-line options such as CBT (level 2) and FFT (level 2), as well as the third-line option IPSRT (level 3), should be based on individual strengths and needs.

4.4 | Pharmacological treatment for acute bipolar depression

Lithium, anticonvulsants, atypical antipsychotics, and other agents such as antidepressants have all been investigated for efficacy in managing bipolar depression. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). Recommendations are summarized in Table 14.

4.4.1 | Step 1: review general principles and assess medication status

Examination of a patient presenting in a depressed state should include an assessment of the nature and severity of depression and associated symptoms, risk of suicide/self-harm behaviour, ability to adhere to a treatment plan, availability of a psychosocial support network, and functional impairment. Laboratory investigations (described in Section 8) should also be completed. Results of the overall assessment should be used to establish the most appropriate treatment setting (eg, ambulatory or inpatient), with consideration given to management of safety risks. Before initiating pharmacological treatment for a depressive episode, it is imperative to rule out symptoms secondary to alcohol/drug use, medications, other treatments, or a general medical condition. Patients should be supported to discontinue stimulant use and limit nicotine, caffeine, drug, and alcohol use. Course of illness and treatments used in current and prior episodes should be assessed, including past response to and tolerability of specific medications and doses, and used to direct subsequent therapeutic choices. Consideration should be given to restarting medications if their recent discontinuation appeared to coincide with a depressive relapse.

Psychoeducation and other psychosocial strategies should also be offered alongside pharmacological treatment to promote ongoing medication adherence, reduce residual symptoms and suicidal behaviour, help identify early signs of relapse, and support functional recovery (see Section 2).

TABLE 14 Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

	Level of evidence by phase of treatment					Considerations for treatment selection				
		Maintenance				Acute		Maintenance		
	Acute depression	Prevention of any mood episode	Prevention of depression	Prevention of mania	Acute mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of manic/ hypomanic switch
First-line treatments										
Quetiapine	●	●	●	●	●	+	++	++	++	–
Lurasidone + Li/DVP	●	◐[a]	◐[b]	◔[c]	n.d.	+	++	++[d]	++/+	–
Lithium	◔	●	●	●	●	+	+	++	++	–
Lamotrigine	◔	●	●	◔	■	++	–	–	–	–
Lurasidone	◔	◔	◔	◔	n.d.	–	+	–	+	–
Lamotrigine (adj)	◔	◔	◔	◔	◪	++	+	++	++	–
Second-line treatments										
Divalproex	◔	●	◔	◐	●	–	+	++[d]	+	–
SSRIs/bupropion (adj)	●	n.d.	◔	n.d.	n.d.	–	+	–	+	+
ECT	◔	◔	◔	◔	◐	+	++	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
Olanzapine-fluoxetine	◔	n.d.	n.d.	n.d.	n.d.	+	++	+++	+	+

adj, adjunctive; DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium, SSRIs, selective serotonin reuptake inhibitors.

●, level 1 evidence; ◕, level 2 evidence; ◐, level 3 evidence; ◔, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◩, level 4 negative evidence; n.d., no data; –, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Trend for superiority on the primary efficacy measure, hence the lower rating.

[b]Effective in those with an index episode of depression.

[c]Negative data from the trial are probably due to methodological issues; rating based on expert opinion.

[d]Divalproex and carbamazepine should be used with caution in women of child bearing age.

[Colour table can be viewed at wileyonlinelibrary.com]

Why are lithium and lamotrigine recommended as first-line agents for bipolar depression?
Reconciling conflicting data

Lithium

In the only large double blind placebo controlled trial conducted to date, lithium was not more effective than placebo for treating acute bipolar depression(254). So, how does one justify recommending lithium as a first-line agent?

The mean serum lithium levels in this study was only 0.61 mEq/L and this may account for lack of efficacy as a previous study demonstrated that lithium monotherapy was as effective as lithium plus paroxetine in those with serum lithium levels of ≥0.8 mEq/L (247).

Further, several small crossover trials demonstrated significantly higher response rates to lithium than placebo in patients with acute bipolar depression (245). As well, the STEP-BD study suggested that mood stabilizers which include lithium are as effective as mood stabilizers plus antidepressants in treating acute bipolar depression, although the durable recovery rate was modest, and there was no sub analysis focusing on lithium versus other antimanic drugs (246). Thus, the findings of these studies justify a Level 2 rating of efficacy for lithium.

Given that lithium also has clearly demonstrated efficacy in preventing mood episodes and in treating acute mania, our hierarchical ranking thus justifies lithium as an important first-line agent for bipolar depression, and based on overall evaluation of available studies, it is our opinion that a trough lithium serum level of 0.8-1.2 mEq/L would be needed for clinical effectiveness.

Lamotrigine

Lamotrigine monotherapy was not superior to placebo in four double blind placebo controlled trials of acute bipolar depression on the primary outcome (254). However, a meta-analysis conducted on the response rates from these studies as well as a BDII trial showed superiority of lamotrigine (248). Moreover, methodological issues with the trials likely led to the effect of lamotrigine being underestimated-including the relatively low final dose (200 mg in most trials, which is lower that usually used in clinical practice) (255) and short trial duration (8 weeks in most trials) which, coupled with the slow titration of lamotrigine, resulted in participants being on the final dose for only a short period (around two weeks). Further, lamotrigine was superior to placebo on Montgomery–Åsberg Depression Rating Scale (MADRS) in one of the studies (249), and changes in symptoms on this scale have since been used to demonstrate the efficacy of other agents for acute bipolar depression. Finally, the addition of lamotrigine to lithium (253) was superior to adding placebo to lithium and there was a trend for superiority of addition of lamotrigine to quetiapine vs placebo add on (252) in treating bipolar depression. It is likely that these beneficial effects are due to the direct effect of lamotrigine and not due to pharmacokinetic interaction between lamotrigine and concomitant medications. Furthermore, trial design issues, especially the fact that the six-week dose titration phase took up most of the 8 week trials, is likely to compromise efficacy signals. Lastly, the short and long-term tolerability of lamotrigine is a major benefit. Taken together, we believe these data justify at least a Level 2 rating for lamotrigine for acute bipolar depression.

In addition to this Level 2 rating for bipolar depression, lamotrigine also has demonstrated efficacy in maintenance treatment and an excellent tolerability profile-features which qualify it to be a first-line treatment for bipolar depression.

FIGURE 2 Lithium and lamotrigine as first-line agents for bipolar I depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

4.4.2 | Step 2: initiate or optimize therapy and check adherence

It is recommended for all patients that pharmacotherapy be initiated with one or more of the available first-line agents. The choice of agent or agents to manage an acute bipolar depressive episode should be discussed with the patient and their supporters (as appropriate) and take into account current and prior medication use and response, personal preference, and the safety and tolerability of each agent, as well as clinical features that may influence prognosis (see "Clinical features that help direct treatment choices").

First-line

Quetiapine (level 1),[241-243] lithium (level 2),[244-246] lamotrigine (level 2)[242,247,248] and lurasidone (level 2)[249] are all recommended as first-line treatment options with evidence for efficacy as monotherapy.

Lurasidone (level 1)[249,250] and lamotrigine (level 2)[251,252] are also recommended as first-line adjunctive treatments (Figure 2). Although quetiapine and lithium have not been assessed for efficacy as adjunctive treatments for acute bipolar depression, clinicians may choose to apply this combination in patients who experience depression when optimized on one of either of these medications.

Recommendations as to which first-line treatment should be considered first are outlined in our hierarchy. We recommend that the agents listed first in the hierarchy be tried first, in the order listed, unless there are patient-specific reasons for choosing an agent lower down in the order, such as previous history of response/ non-response or clinical features (see Clinical features which help direct treatment choices). For instance, if a patient presents with an acute bipolar depressive episode and is not taking any treatment and has not been treated for this episode, that patient should be commenced on quetiapine monotherapy if there is no previous history of non-response or tolerability concerns with quetiapine. However, if a patient had been taking lithium and either had a breakthrough acute bipolar depressive episode or did not respond to monotherapy with lithium, then lurasidone or lamotrigine or quetiapine add-on or switch to quetiapine monotherapy or lurasidone monotherapy might be more appropriate in that order, given that lurasidone and lamotrigine adjunctive therapies have demonstrated efficacy in lithium non-responders. Similarly, in non-responders to lithium monotherapy, adjunctive lamotrigine could be another option.

Clinicians are advised to appropriately dose these medications for an adequate period of time before concluding lack of efficacy. Clinical trials have shown that there is no difference in efficacy between quetiapine 300mg and 600mg daily doses. Lower doses of quetiapine have not been studied in clinical trials for bipolar depression. Therefore, clinicians are advised to consider a target dose of 300 mg/day for quetiapine. For lithium, we suggest that serum lithium levels should be maintained between 0.8 and 1.2 meq/L, while for lamotrigine, the target should be a minimum of 200 mg/day.

4.4.3 | Step 3: add on or switch therapy (alternate first-line agents)

Across several different medications for bipolar depression, early improvement (after 2 weeks) has been found to be a reasonable predictor of overall response, whereas lack of early improvement is a more robust predictor of non-response.[255] Lamotrigine is the exception to this rule, given a necessary slow titration initiating the medication. In the case of non-response, dosing should be optimized and issues of non-adherence identified and addressed (see Section 2) prior to adjusting treatment strategies.

When determining whether an agent should be switched or another first-line agent be added on to any current treatment, the effectiveness of each of the medications needs to be understood in the context of all the goals of managing BD. It is often the case that a medication may be selected to address several goals; for instance, lithium could be added for acute depression with intent to also bolster anti-manic prophylaxis. In this scenario, if lithium is ineffective in the individual patient for an acute bipolar depression but is also being used over the long term for anti-manic prophylaxis, then an "add-on" intervention should be the next treatment for the acute bipolar depression. If, for instance, the anti-manic prophylaxis is already being fully provided by an atypical antipsychotic, then the new medication could replace lithium via a switch strategy. Decision-making must also address efficacy for comorbid conditions, as well as tolerability concerns. In principle, all things being equal, a switch is preferred over add-on to limit the degree of polypharmacy, but the clinical reality is that medications may be helpful for some but not all components of the illness, and using rational polypharmacy via add-on treatments is often required. For situations in which patients experience a depressive episode while already receiving an adequately dosed antidepressant, strong consideration should be given to discontinuing or switching the class of antidepressant, unless clear benefits are apparent in reducing the severity or frequency of depressive episodes. Switch of medications should be done in an overlap and taper manner unless there is medical necessity for abrupt discontinuation.[257]

All first-line options should be tried in adequate doses for an adequate duration of time before considering second-line options either as an add-on or switch strategy.

4.4.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

In patients who are inadequately responsive to first-line agents, monotherapy with divalproex (level 2)[242,258] is included as a second-line option.

Adjunctive use of antidepressant therapy (selective serotonin reuptake inhibitors [SSRIs] or bupropion) with lithium/divalproex or an atypical antipsychotic may also be considered as a second-line add-on treatment. While some individual studies have failed to demonstrate the efficacy of adjunctive antidepressant therapy, a recent meta-analysis (level 1) supports efficacy, albeit with a small effect size.[259]

This is a key aspect of decision-making regarding antidepressants, since historically much of the focus has been on risk of manic switch or rapid cycling, with an underappreciation of the relatively weak efficacy data. This new appreciation, exemplified by the small benefit seen in the above meta-analysis, led to the change from the last CANMAT guidelines, which previously gave add-on SSRI/bupropion antidepressants a first-line recommendation. As per the ISBD Antidepressant Task Force recommendations,[260] antidepressants should ideally be avoided, or used cautiously if necessary, in patients with a history of antidepressant-induced mania or hypomania, current or predominant mixed features, or recent rapid cycling. Patients and caregivers (as appropriate) should receive education regarding early warning symptoms of mood switching or cycle acceleration, and antidepressants should be discontinued if these emerge. Antidepressant *monotherapy* should NOT be used for the treatment of BDI depression.

ECT (level 3) is also a second-line treatment, and should be considered particularly for treatment-refractory patients and those for whom a rapid treatment response is needed, such as those with severe depression with imminent suicidal risk, catatonia or psychotic depression,

Why are armodafinil and modafinil third-line treatments for bipolar I depression?

Armodafinil adjunctive therapy was assessed in three double blind randomized controlled trials. Of these, one was positive (270) but in the other two studies, it failed to separate from placebo on the primary efficacy measure (286, 287) although in one of the trials several secondary outcomes were positive (288). Furthermore, in a fourth trial, there was also suggestion of efficacy based on some secondary measures (289). Therefore, although two trials were negative on the primary efficacy measure, based on one positive trial and some positive secondary outcomes in two trials, this was given a Level 4 rating (expert opinion), and recommended as a third-line.

Although modafinil has been shown to be efficacious in the only trial (269), it was also recommended a third-line in light of the three negative trials for armodafinil.

FIGURE 3 Armodafinil and modafinil as third-line agents for bipolar I depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 15 Additional agents evaluated for use in acute bipolar I depression

	Agent	Level of evidence
Third-line	Aripiprazole (adj)	Level 4
	Armodafinil (adj)	Level 4
	Asenapine (adj)	Level 4
	Carbamazepine	Level 2
	Eicosapentaenoic acid (EPA) (adj)	Level 2
	Ketamine (IV) (adj)	Level 3
	Light therapy +/− total sleep deprivation (adj)	Level 3
	Levothyroxine (adj)	Level 3
	Modafinil (adj)	Level 2
	N-acetylcysteine (adj)	Level 3
	Olanzapine	Level 1
	Pramipexole (adj)	Level 3
	Repetitive transmagnetic stimulation (rTMS) (adj)	Level 2
	SNRI/MAOI (adj)	Level 2
Not recommended	Antidepressant monotherapy	Level 2 negative
	Aripiprazole	Level 1 negative
	Lamotrigine + folic acid	Level 2 negative
	Mifepristone (adj)	Level 2 negative

adj, adjunctive; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

and/or when a rapid response is important for medical stabilization. Data support efficacy for brief pulse right unilateral placement, although there are insufficient data to guide the decision of unilateral or bilateral placement for bipolar depression.[261] Additional second-line options include cariprazine, with efficacy demonstrated through a large RCT[262] and a pooled analysis of a failed RCT and a positive RCT[263] (level 2), although there is less clinical experience supporting its use. Olanzapine-fluoxetine combination (level 2)[264,265] is effective and is also recommended as a second-line option.

Similar to the approach for treatment of a manic episode, multiple first- and second-line agents and combinations should be trialled before considering initiating third-line agents in step 5.

4.4.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Third-line options are listed alphabetically in Table 15. In patients who fail to respond to multiple first- and second-line agents, third-line choices include monotherapy with carbamazepine (level 2)[242] or olanzapine (level 1).[242]

Agents that may be applied adjunctively include aripiprazole (level 4),[266,267] armodafinil (level 4)[268,269] (Figure 3), asenapine (level 4),[270] levothyroxine (level 3),[271,272] modafinil (level 2)[268] (Figure 3), and pramipexole (level 3).[273,274] rTMS targeted at the left or right dorsolateral prefrontal cortex (level 3)[275] may also be used in addition to medication. Other classes of antidepressants such as serotonin-norepinephrine reuptake inhibitors [SNRIs] and monoamine oxidase inhibitors [MAOIs] could be used adjunctively but clinicians need to ensure adequate anti-manic prophylaxis in such situations, as SNRIs and MAOIs have a higher propensity than other antidepressants to induce manic switch and cause mood destabilization (level 2).[276-278]

Ancillary treatments such as adjunctive eicosapentaenoic acid (EPA) (level 2),[169,279,280] *N*-acetylcysteine (level 3),[281] and light therapy (level 3),[282] including bright light delivered midday (level 3),[283] are also recommended as third-line treatment options to use adjunctively to other medications. There may be additional benefits to using light therapy in combination with total sleep deprivation (level 2), although there is little clinical experience with this technique. While there is evidence from several small studies that intravenous ketamine (level 3)[284] is a highly effective and fast-acting antidepressant, due to its invasive nature, short duration of effect, and lack of long-term safety data, it has been relegated to a third-line treatment, with recommendations that it be reserved for patients with severe symptoms or significant suicidal ideation for whom other treatments have been unsuccessful. In clinical situations that prioritize rapidity of response to treatment, ketamine may be considered earlier in the treatment order, although clinicians need to be aware that the data for efficacy are limited and the effects do not appear to last longer. Further, there are case reports of manic switch, but the clinical trial data have not provided any confirmatory evidence.[284] Also, clinicians need to be aware of potential abuse of ketamine, especially in domiciliary use situations.[285]

4.4.6 | Agents not recommended for the treatment of acute bipolar depression

Antidepressants should not be used as monotherapy in patients with BDI depression, as available trials do not support their efficacy and there are concerns about their safety in terms of mood switching (level 2 negative).[260,289-291]

Aripiprazole monotherapy failed to separate from placebo in two bipolar depression trials.[292] Although the pooled analysis reported separation,[293] the mean difference in Montgomery–Åsberg Depression Rating Scale (MADRS) change score was only 1.12 points, which is not clinically meaningful and it is thus not recommended (level 1 negative). Ziprasidone monotherapy or adjunctive therapy (level 1 negative),[242,294] lamotrigine in combination with folic acid (level 2 negative),[251] and mifepristone (adjunctive) (Leve 2 negative)[295] are also not recommended due to evidence for lack of antidepressant efficacy (Table 15).

4.4.7 | No specific recommendation/agents that require further study

There are insufficient data to make a recommendation regarding the use of aspirin (adjunctive) (level 3 negative),[296] celecoxib (adjunctive)

(level 3 negative),[297] gabapentin (monotherapy) (level 3 negative),[298] leviteracitam (adjunctive) (level 3 negative),[299] lisdexamfetamine (adjunctive) (level 3 negative),[300] memantine (adjunctive) (level 3),[301] pioglitazone (adjunctive) (level 3),[302,303] riluzole (level 4 negative),[304] and risperidone (adjunctive) (level 3).[305] Although adjunctive therapy with pregnenolone separated from placebo at week 6, the change in depressive symptoms was not significantly different from week 8 to week 12 between the two groups (level 2).[306]

4.5 | Clinical features that help direct treatment choices

There are limited data on predictors of treatment response in bipolar depression. However, clinical features of a depressive episode including DSM-5 specifiers may assist clinicians in choosing among recommended treatment options.

Need for rapid response

Amongst the first-line options recommended, quetiapine and lurasidone have separated from placebo in clinical trials at as early as week 1.[249,307,308] Thus, these medications may be preferable when a rapid response is required, for example in patients who are at increased risk of suicide or who have medical complications, including dehydration. While ECT is recommended as a second-line option, this may also be used earlier when a rapid response is imperative. Second-line options such as cariprazine and olanzapine-fluoxetine have also separated from placebo at as early as week 1 and may also be considered when a rapid response is desirable, but this needs to be balanced against the potential side effects. Lamotrigine administration requires slower titration due to the risk of skin rashes, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and is thus not ideal for patients requiring a rapid response. Lamotrigine, however, is well tolerated, and there is some evidence that its effectiveness may be more pronounced in patients experiencing depressive cognitions and psychomotor slowing.[309]

Previous treatment response

Adjunctive antidepressant use may be appropriate in those with prior antidepressant response if there was no history of treatment-emergent switch.[310]

Anxious distress

Symptoms of anxiety are often experienced during a depressive episode, and are predictive of more persistent depressive symptoms[311] and increased suicidal ideation.[312] A pooled analysis of two double-blind RCTs demonstrated that quetiapine is more effective than placebo in relieving symptoms of anxiety co-occurring alongside bipolar depression,[313] and olanzapine-fluoxetine combination has also been shown to be effective.[314] In a post hoc analysis, lurasidone was effective in improving depressive as well as anxiety symptoms in patients with MDD who had mixed features and anxiety.[315] The anxiolytic effects of divalproex, risperidone, and lamotrigine appear to be limited.[199,316]

Mixed features

Many patients with bipolar depression will also experience at least subsyndromal hypomanic or manic features, and this presentation is associated with more severe depressive symptoms, as well as a higher rate of substance use and cardiovascular disease.[317] For many of these patients, combination therapy will be necessary to adequately address symptoms.[318] Pooled analysis indicates that atypical antipsychotics show a class effect in alleviating mixed features in bipolar depression, with olanzapine-fluoxetine combination, asenapine, and lurasidone all demonstrating efficacy.[319] Lurasidone has further been shown to have efficacy in treating both depressive and hypomanic symptoms in MDD with mixed features.[320] The ISBD Task Force recommends avoiding antidepressants in patients with mixed features[260] and the CANMAT/ISBD group concurs with this recommendation.

Melancholic features

No specific studies assessed the predictive ability of melancholic features; however, clinical experience suggests that ECT is very effective in this population.

Atypical features

There is some evidence for efficacy of tranylcypromine in patients with anergic bipolar depression.[321] However, given the risks of potential manic switch, this agent should only be used in conjunction with lithium or divalproex or an atypical antipsychotic. Clinicians also must consider adverse events of this agent related to its interactions with food and other medications.

Psychotic features (mood congruent or incongruent)

Up to 20% of inpatients experience psychosis in the context of an acute bipolar depressive episode.[322] The relative efficacy of various medications to treat these features in this phase of illness has not been examined, although clinical experience suggests that ECT and antipsychotics are highly effective for this population.

Rapid cycling

As described in Section 3, hypothyroidism, antidepressants and substance abuse may be associated with rapid cycling, thus making assessment of thyroid function and discontinuation of antidepressants, drugs of abuse, stimulants, and other psychotropic agents imperative. As there is no evidence to support any specific agent to treat acute depression during a rapid cycling phase, appropriate pharmacotherapy should be selected based on effectiveness in the acute and maintenance phases. Lithium, divalproex, olanzapine, and quetiapine all appear to have comparable maintenance efficacies in these patients.[219] In contrast, lamotrigine did not separate from placebo in maintenance treatment in patients with rapid cycling BDI.[323] Antidepressants are not recommended, as they have been shown to destabilize patients, even with concurrent mood stabilizer use.[324]

Seasonal pattern

While some individual patients may show a seasonal pattern, Canadian data are mixed as to whether episodes of mania or depression in BD

TABLE 16 Risk factors for partial adherence or non-adherence to medication

Sociodemographics	Male, younger age, low level of education, single
Psychological	Poor insight, lack of awareness of disease, negative attitude to treatment, fear of side effects, negative attitude to medication, low overall life satisfaction, low cognitive functioning
Comorbidity	Alcohol or cannabis use, obsessive compulsive disorder
Social	No social activities, work impairment
Chronology	Younger age of onset, current inpatient status, hospitalization or suicide attempt in past 12 months
Disease characteristics	Mixed episode, rapid cycling, delusions and hallucinations, greater severity of illness, BDI diagnosis, higher number of episodes
Treatment-related factors	Side effects of medications, inadequate efficacy of medication, use of antidepressants, low treatment doses

Adapted from Leclerc et al.[353]

follow a consistent seasonal variation.[222] There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

5 | MAINTENANCE THERAPY FOR BIPOLAR DISORDER

5.1 | Need for long-term strategies

Almost all individuals with BD require maintenance treatment to prevent subsequent episodes, reduce residual symptoms, and restore functioning and quality of life. There is increasing evidence to suggest that, for a subgroup of patients, BD may be a neuroprogressive disease in which recurrences are associated with reductions in brain grey and white matter volumes, worsening cognitive impairment, a decrease in inter-episodic recovery and functioning, a higher rate and severity of relapse, and a reduced rate of treatment response to both pharmacotherapy and psychotherapy.[325] It is therefore important that comprehensive treatment be initiated even after a first episode.[63] Effective maintenance treatment, early in the course of illness, has been shown to reverse cognitive impairment and preserve brain plasticity, particularly in those who remain episode free,[326,327] and may therefore lead to improved prognosis and minimization of illness progression.[328] There are preliminary data suggesting that, after a first episode, lithium might be superior to quetiapine in both volumetric and cognitive outcomes.[329,330]

With treatment, 19%-25% of patients will experience a recurrence every year, compared to 23%-40% of those on placebo.[331] Risk factors for recurrence include younger age of onset,[332] psychotic features,[212] rapid cycling,[331] more (and more frequent) previous episodes,[333] comorbid anxiety,[334] and comorbid SUDs.[335] Persistent subthreshold symptoms also increase risk for subsequent mood episodes,[334,336,337] and the presence of residual symptoms should therefore be an indicator of a need for further treatment optimization. Availability of psychosocial support and lower levels of stress are also protective against recurrence.[337,338]

5.2 | Treatment adherence

Concordance between clinician and patient views of illness and treatment is a crucial determinant of adherence,[339] and reinforces the need for a collaborative approach to the treatment alliance.[340] Asking about adherence behaviour and attitudes in a non-judgemental manner and exploring the reasoning behind poor adherence are important parts of treatment,[341] as up to half of patients do not take their medications as prescribed.[342-344] Unrecognized treatment non-adherence can lead physicians to believe that the patient is non-responsive, resulting in unnecessary dose increases (especially problematic for drugs with a narrow therapeutic index), medication switches, or adjunctive medications.[341] Treatment withdrawal may precipitate recurrence; 50%-90% of patients discontinuing lithium experience a recurrence within 3-5 months,[345,346] with rapid lithium discontinuation associated with greater recurrence risk than gradual discontinuation.[347] Withdrawal of other mood stabilizers also predicts recurrence.[348,349] Risks for hospitalization, suicide, and lost productivity are also increased with non-adherence or discontinuation.[350-352] A variety of patient, disorder, and treatment-related risk factors for non-adherence or partial adherence are outlined in Table 16.[353]

Meta-analyses suggest that interventions aimed at engaging patients in treatment may more than double adherence compared to treatment as usual or other control groups.[354] Brief psychoeducational interventions focusing specifically on medication adherence can be integrated into clinical practice.[354] Flexible and collaborative engagement to address individual risk factors for non-adherence is recommended to optimize acceptability of pharmacological therapies.[353,355-357]

5.3 | Psychosocial interventions for maintenance therapy

Although pharmacotherapy is the foundation of maintenance treatment in BD, it is often insufficient to prevent recurrence. Over the last two decades, several controlled trials have examined the efficacy of adjunctive psychosocial treatments in reducing recurrence. On average, adjunctive psychosocial treatments reduce recurrence rates by about 15%. Therefore, adjunctive psychosocial interventions are an important component of management of BD and should be offered for all patients.

As described in more detail in Section 2, psychoeducation is the only first-line psychosocial intervention for the maintenance phase (level 1), which should be offered to all patients. Additional second-line options such as CBT (level 2) and FFT (level 2), and third-line options such as IPSRT (level 2) and peer support (level 2) should be offered based on individual strengths and needs.

5.4 | Efficacy ratings for pharmacological agents used as maintenance therapy: importance of naturalistic and cohort studies

Evidence from RCTs is at the core of the recommendations in these guidelines. Nonetheless, RCTs are not the only source of clinically useful information, particularly when evaluating maintenance therapy. RCTs offer relatively limited follow-up time-frames while, for some patients, maintenance therapy may extend across decades. Furthermore, new medications are often assessed in studies with an enriched design (including only patients who have responded to the medication under study in the acute phase), limiting the generalizability of positive findings to patients who responded to the medication acutely.

Useful data can be obtained from large, often whole-population databases constructed from electronic medical records or electronic patient registries with large numbers of patients that would be difficult to obtain in RCTs. In some instances, they allow comparisons of multiple treatments.[358-360] These large numbers make it possible to evaluate differences in rates of rare events such as less common side effects or suicide.[361,362]

Patient cohorts followed in a specific setting provide another source of informative data. Their main advantage usually is the length of observation, in some instances reaching several decades.[363-365] This comes at the cost of generalizability, in terms of both patient selection and non-random treatment allocation.

5.5 | Pharmacological treatments for maintenance therapy

As in earlier sections, pharmacological treatments for maintenance therapy have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). Results are summarized in Table 17.

5.5.1 | Step 1: review general principles and assess medication status

Many agents recommended for management of acute manic or depressive episodes have prophylactic efficacy. Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase. However, there are exceptions to this: the efficacy of adjunctive antidepressant therapy has not been examined systematically in large double-blind placebo-controlled trials; hence, long-term antidepressant use is not recommended, especially in light of the concerns about potential risk of manic/hypomanic switch and mood instability. However, in the subgroups of patients who have responded to combination treatment and are stable, preliminary evidence suggests that withdrawal of antidepressants may contribute to destabilization.[366]

Clinical trials have shown that many atypical antipsychotics are effective in preventing relapse of mood episodes; with many agents, this efficacy is related to prevention of manic episodes but not depressive episodes. However, many of these trials have been conducted in patients with an index manic episode and, given that the polarity of an index episode predicts the polarity of relapse, depressive relapse rates in placebo groups in such studies have been low- compromising the statistical power to test the efficacy of these agents in prevention of depressive relapses. Thus, the efficacy of many of these agents in preventing depressive relapses remains unknown.

For patients who are currently not receiving or responding to pharmacological treatment, a careful history including details of clinical course, response (or lack thereof) to previously used medications, and family history should be collected. Other variables to be considered include psychiatric comorbidity (including substance use), the predominant illness polarity, and the polarity of the most recent episode.

Ongoing clinical monitoring, including medication blood levels as appropriate, is also a crucial part of maintenance treatment that should be used to support enhanced medication adherence, detection of early symptoms of recurrence, and monitoring of side effects (see Section 8).

5.5.2 | Step 2: initiate or optimize therapy and check adherence

The choice of agent or agents used in maintenance treatment should be discussed with the patient and their caregivers (as appropriate) and, based on knowledge of current and prior medication use and response, safety and tolerability of each agent, predominant episode polarity, and clinical features that may influence prognosis (see "Clinical features that help direct treatment choices"). As with treatment for mania and acute depression, we recommend that treatment choices for maintenance treatment of BD should follow the hierarchy listed in Table 17 unless patient preference or other considerations such as previous response/non-response, tolerability or predominant polarity justify other choices. Similarly, as a general rule, if a patient has been treated for an acute mood episode and responded to a first-line maintenance treatment, we recommend continuing that treatment for maintenance even if lower down in the hierarchy. As an example, if a patient responded to asenapine in an acute manic episode, asenapine should be continued, even if it is lower down in the hierarchy for maintenance treatment. It may be necessary to lower the dose to some degree once in maintenance treatment as patients often experience greater side effects once out of the acute episode.

There is evidence that the risk of recurrence is reduced when an antipsychotic is combined with lithium/divalproex. When a combination therapy of an atypical antipsychotic with lithium/divalproex was used to treat acute mania, continuing the atypical antipsychotic for the first 6 months following response offered clear benefit in reducing risk of mood episode recurrence (level 2),[367] but the benefits beyond 6 months remain uncertain. Therefore, clinicians are advised to re-evaluate risks and benefits after 6 months of sustained response to determine whether maintenance combination therapy with an atypical antipsychotic is justified.

TABLE 17 Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

	Level of evidence by phase of treatment					Considerations for treatment selection			
	Maintenance			Acute		Acute		Maintenance	
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Lithium	●	●	●	◕	●	+	+	++	++
Quetiapine	●	●	●	●	●	+	++	++	++
Divalproex	●	◕	◐	◕	●	–	+	++[c]	+
Lamotrigine	●	●	◕	●	■	++	–	–	–
Asenapine	◕	◕	◕	n.d	●	–	+	–	+
Quetiapine + Li/DVP	●	●	●	◕	●	+	++	+++[c]	++
Aripiprazole + Li/DVP	◕	n.d.[a]	◕	◕	◕	+	+	++[c]	++
Aripiprazole	◕	n.d.[a]	◕	■	●	–	+	–	+
Aripiprazole OM	◕	n.d.[a]	◕	n.d.	n.d.	–	+	–	+
Second-line treatments									
Olanzapine	●	●	●	●[b]	●	+	++	+++	++
Risperidone LAI	●	n.d.[a]	●	n.d.	n.d.	–	+	+	++
Risperidone LAI (adj)	◕	◕	◕	n.d.	n.d.	+	++	+++	++
Carbamazepine	◕	◕	◕	◐	●	++	++	+[c]	++
Paliperidone (>6 mg)	◕	n.d.[a]	◕	n.d.	●	–	+	+	++
Lurasidone + Li/DVP	◐[d]	◐[e]	◕	◕	n.d.	+	++	++[c]	++/–
Ziprasidone + Li/DVP	◕	n.d.[a]	◕	◧	◧	++	++	++[c]	+

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.

●, level 1 evidence; ◕, level 2 evidence; ◐, level 3 evidence; ◔, level 4 evidence; ■, level 1 negative evidence; ◧, level 2 negative evidence; ◧, level 3 negative evidence; ◧, level 4 negative evidence; n.d., no data; – limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Did not separate from placebo in those with index mania; no studies available in index depression.

[b]Did not separate on core symptoms of depression.

[c]Divalproex and carbamazepine should be used with caution in women of child bearing age.

[d]Trend for superiority on the primary efficacy measure, hence the lower rating.

[e]Effective in those with an index episode of depression.

[Colour table can be viewed at wileyonlinelibrary.com]

Why is divalproex recommended as a first-line maintenance treatment for bipolar I disorder?

In the only large double-blind placebo controlled RCT of divalproex monotherapy (373), it was not more effective than placebo in preventing relapse of mood episodes i.e. time to any mood episode. However, in this trial, lithium which has been shown in many other studies to be effective in relapse prevention, was also found to be no more effective than placebo. Thus, these results suggest that this trial was a failed trial and not a negative trial.

Most modern studies of maintenance therapy use enriched design, meaning that those that responded in acute phase to the medication being tested are randomized to continuation of the same drug or replacement with placebo. This practice to a large extent mirrors clinical practice as clinicians are likely to continue the medication that worked in the acute phase for maintenance treatment. Interestingly, in the divalproex RCT, some but not all patients that were randomized into the double-blind phase were divalproex responders. In a post-hoc analysis of this study, in this enriched subgroup of patients that responded to divalproex during the acute phase and randomized to continuation of divalproex vs switch to placebo, divalproex was more effective in preventing relapse of mood episodes compared with placebo.

Further, divalproex was superior to placebo on a number of other secondary efficacy measures such as lower rates of discontinuation for any mood episode or a depressive episode. Surprisingly, there was also a trend for superiority of divalproex relative to lithium in time to any mood episode. Other RCTs have shown that divalproex is as effective as lithium (221) in preventing relapse of mood episodes.

As well, two meta-analysis have concluded that divalproex is effective in preventing relapse of mood episodes (370, 372), and a population based cohort study in the UK showed that there were no differences in efficacy between divalproex, quetiapine and olanzapine in the maintenance treatment of bipolar disorder (359).

Taken together, we believe these efficacy data support our rationale for a Level 1 rating. This along with clinical experience, real world cohort data, and safety, justify our recommendation of divalproex as a first-line maintenance treatment.

FIGURE 4 Divalproex as a first-line maintenance therapy for bipolar I disorder: Summary of evidence
RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

First-line

Lithium (level 1),[368,369] quetiapine (level 1),[369,370] divalproex (level 1) [369,371,372] (Figure 4) and lamotrigine (level 1)[369,373] monotherapies have the best combination of clinical trials, administrative data, and clinical experience to support their use as first-line therapies for maintenance treatment of BD. Recent data suggest that asenapine (level 2)[374] is effective in preventing both manic and depressive episodes, and thus is recommended as a first-line treatment. Finally, aripiprazole oral (level 2)[375,376] or once monthly (level 2)[377] is also recommended as a first-line monotherapy in view of its efficacy in preventing any mood or manic episode as well as its safety/tolerability profile, although it has not been shown to be effective in preventing depression.

Additional combination therapies included as first- line include quetiapine adjunctive therapy with lithium/divalproex (level 1),[378,379] which has demonstrated efficacy in preventing any mood, manic or depressive episode. Aripiprazole plus lithium/divalproex (level 2)[380] should also be considered as a first-line option.

TABLE 18 Additional agents evaluated for use in maintenance treatment of bipolar I disorder

	Agent	Level of evidence
Third-line	Aripiprazole + lamotrigine	Level 2
	Clozapine (adj)	Level 4
	Gabapentin (adj)	Level 4
	Olanzapine + fluoxetine	Level 2
Not recommended	Perphenazine	Level 2 negative
	Tricyclic antidepressants	Level 2 negative

adj, adjunctive.

For patients who experience a recurrence or who remain symptomatic while on a first-line agent or a combination, dosing should be optimized and issues of non-adherence identified and addressed prior to moving to step 3.

5.5.3 | Step 3: add on or switch therapy (alternate first-line agents)

If therapy with one or a combination of the first-line agents at optimal doses is inadequate or not tolerated, the next step is to switch to or add on an alternate first-line agent. Because there are multiple first-line agents with substantial efficacy data and relative safety and tolerability, the use of second-line agents is only recommended after unsuccessful trials of multiple first-line strategies.

5.5.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

Although olanzapine (level 1)[381,382] is effective in preventing any mood, manic or depressive episode, it is considered second-line treatment because of safety issues such as metabolic syndrome. Biweekly long-acting injectable risperidone monotherapy (level 1)[383] or adjunctive therapy (level 2)[384] has demonstrated efficacy in preventing any mood or manic episode, but had no clear efficacy in depressive episode prevention in these trials. Further, there was a trend for superiority of oral risperidone adjunctive therapy at 6 months in preventing any mood episode and in preventing mania but not depression.[367] Carbamazepine (level 2) has not been assessed in any large placebo-controlled trials, but active comparator trials support its efficacy.[385] Paliperidone (level 2) was more effective than placebo

in preventing any mood or manic episode but less effective than olanzapine.[386]

Ziprasidone oral adjunctive therapy (level 2)[387] has been shown to be effective in preventing any mood or manic episode, although there are conflicting (positive and negative) data for acute treatment (see Sections 3 and 4). There was a trend for superiority of lurasidone adjunctive therapy in preventing any mood episode (but not manic or depressive episodes individually) in a controlled trial with significant separation from placebo in preventing mood episodes in those with an index depressive episode.[388] Thus, lurasidone adjunctive therapy may be appropriate for those who responded to this medication during an index depressive episode.

5.5.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Third-line agents are listed alphabetically in Table 18. There was a trend for superiority of adjunctive aripiprazole with lamotrigine (level 2)[389] compared to lamotrigine monotherapy in preventing mania; thus, this combination may provide additional prophylaxis for patients on lamotrigine monotherapy in preventing manic relapses. Clozapine (level 4)[162] and gabapentin (level 4)[390] may also be useful adjunctive treatments for those who incompletely respond to first- or second-line therapies. The olanzapine/fluoxetine combination appears to maintain mood stability over a 6-month period in patients with bipolar depression who respond acutely to this combination (level 2).[391]

5.5.6 | No specific recommendation/agents that require further study

We do not provide specific recommendations for the use of cariprazine, as there is currently only evidence for efficacy in acute manic and depressive episodes[262,392] and not yet for maintenance treatment (level 4). While a small RCT suggests a lack of efficacy for flupenthixol as maintenance treatment, larger studies are needed before definite conclusions can be drawn (level 3 negative).[393] Likewise, oxcarbazepine adjunctive therapy requires further evaluation (level 4).[394-396] No recommendation is made for topiramate as there is an absence of controlled data supporting its efficacy in maintenance (level 4 negative), and a lack of efficacy in acute mania[381]; however, its use may be indicated as it has efficacy for many syndromes that are often comorbid with BD (Section 7).

5.5.7 | Agents not recommended for maintenance treatment

Perphenazine is not recommended for maintenance based on evidence that patients treated with perphenazine and a mood stabilizer following an episode are more likely to have emergent depressive symptoms or intolerable side effects, compared to those maintained on the mood stabilizer alone (level 2 negative).[397] Tricyclic antidepressant mono or adjunctive maintenance therapy is not recommended due to an increased risk of manic switch (level 2 negative)[398-400] (Table 18).

5.5.8 | Clinical features that direct treatment choices

Clinical trials tell us how efficacious one drug is in comparison with another (or placebo) in groups of patients. To determine the degree of long-term response in an individual patient requires a different evaluation and may take a considerable amount of time. Few patients manage a lifetime of BD with monotherapy—most will require short- or long-term combination therapies to address acute or subsyndromal symptoms as well as to reduce rates of recurrence. Some,[359,401,402] but not all,[403,404] reports suggest that long-term treatment becomes less effective with longer duration of untreated illness, an argument for finding an effective treatment as early as possible.

In most instances, it is difficult to differentiate nonspecific correlates of good prognosis of the illness from factors specific to the response to a particular mood stabilizer. Available data come mostly from naturalistic/cohort studies and few randomized trials.[405] Nevertheless, several tentative predictors are emerging from the available data.

Factors associated with overall good prognosis of BD include good treatment adherence, lack of early adversity, intermediate age at onset, good social support, and the absence of spontaneous rapid cycling[406,407] or features of a personality disorder.[408]

In general, lithium is the gold standard for maintenance treatment, as it is effective in preventing both manic and depressive episodes (magnitude of prophylactic efficacy greater against mania vs depression) and appears to have a degree of anti-suicidal effects.[352,369,409-413] Patients who respond well to lithium treatment usually have an episodic remitting pre-treatment clinical course, a family history of BD (especially BD responsive to lithium), low rates of comorbidity (especially anxiety and substance abuse disorders), and a pattern of mania-depression-euthymia in biphasic episodes, as well as a typical clinical presentation.[414-416] Responsiveness may also be a familial trait, with a study showing that patients who have a lithium-responsive relative have a 67% likelihood of also being lithium responsive, versus 35% of those without a responsive relative.[417] Among biological measures, lack of electroencephalogram (EEG) abnormalities, higher brain lithium concentration, increased *N*-acetyl aspartate and lower myo-inositol peaks on magnetic resonance spectroscopy, as well as several variants in candidate gene studies, may predict response,[418] but these studies require confirmation. Response to lithium in particular seems to be quite specific, as shown in a study of neurons derived from induced pluripotent stem cells. The neurons from people with BD were hyperexcitable and their activity was selectively modified by *in vitro* lithium in accordance with clinical response.[419]

Responders to lamotrigine have a predominantly depressive polarity as well as comorbid anxiety.[420,421] Lamotrigine monotherapy is not appropriate for patients with frequent manic episodes, as it has limited efficacy in preventing mania.

Quetiapine has been shown to be effective in preventing manic, depressive and mixed episodes in patients with index manic, depressive and mixed episodes, and thus may be particularly valuable in those with mixed features.[422] Asenapine appears to be effective in preventing both mania and depression, although the magnitude of prophylactic efficacy is greater for mania relative to depression. In a randomized open trial of carbamazepine versus lithium, responders to carbamazepine were more likely to have an atypical illness, BDII or schizoaffective disorder.[405]

Data to differentiate anti-psychotic medication responders from non-responders are lacking.

Overall, some of these possible predictors can have clinical utility, but not all are practical. For instance, it is difficult to evaluate a pre-treatment course in patients who started their treatment after one or two episodes (practice recommended by most treatment guidelines), and biomarkers are intriguing but lack sufficient replication and are not readily available.

In patients with a history of a rapid cycling course, as indicated in previous sections, factors associated with rapid cycling must be addressed. These include discontinuation of stimulants and antidepressants and treating hypothyroidism if present. With regard to treatment options, the evidence suggests that monotherapy with a single mood stabilizer is often ineffective and patients may require a combination of mood stabilizers to achieve mood stability.

Treatment-refractory bipolar disorder

Treatment refractoriness may be related to non-adherence to oral medications, failure to optimize evidence-based oral medication therapy/therapies, comorbidities complicating therapeutic response or true resistance to pharmacotherapy. Clinicians are advised to make a comprehensive assessment to determine factors responsible for treatment refractoriness. Adequate doses of first and second-line agents should be employed for an adequate period of time (eg, this is typically individualized based on the previous course of mood episodes in each patient) to assess prophylactic response. Comorbidities should be addressed with pharmacological or psychological strategies as appropriate. While genotyping for cytochrome P450 enzymes such as 2D6 and 3A4 which metabolize most psychotropic drugs is not routinely recommended, clinicians are advised to consider this in patients with refractory BD who have not responded to high doses of various first, second, and third-line treatments or their combinations in order to exclude the possibility of ultra rapid metabolic status contributing to poor response.

In patients who are non-adherent, psychosocial strategies such as psychoeducation should be used to improve treatment adherence. If ineffective, long-acting injectable medications should be offered. Risperidone long-acting injectable monotherapy[383] or adjunctive therapy (level 2)[384] once every 2 weeks or aripiprazole once-monthly injectable monotherapy (level 2)[377] has been shown to be effective in preventing relapse of mood episodes in patients with BD.

There is a dearth of clinical trial data to inform treatment options for management of patients with refractory BD. Clozapine adjunctive therapy has been shown to be effective in reducing symptoms and total medication use in treatment-resistant patients.[162]

TABLE 19 Strength of evidence and treatment recommendations for acute management of bipolar II depression

Recommendation	Agent	Level of evidence
First-line	Quetiapine	Level 1
Second-line	Lithium	Level 2
	Lamotrigine	Level 2
	Bupropion (adj)	Level 2
	ECT	(Level 3)
	Sertraline[a]	Level 2
	Venlafaxine[a]	Level 2
Third-line	Agomelatine (adj)	Level 4
	Bupropion (adj)	Level 4
	Divalproex	Level 4
	EPA (adj)	Level 4
	Fluoxetine[a]	Level 3
	Ketamine (IV or sublingual) (adj)[c]	Level 3
	N-acetylcysteine (adj)	Level 4
	Pramipexole (adj)	Level 3
	T3/T4 thyroid hormones (adj)	Level 4
	Tranylcypromine	Level 3
	Ziprasidone[b]	Level 3
Not recommended	Paroxetine	2 negative

adj, adjunctive; ECT, electroconvulsive therapy; EPA, eicosapentaenoic acid.
[a]For patients with pure depression (non-mixed).
[b]For patients with depression and mixed hypomania.

6 | BIPOLAR II DISORDER

6.1 | Presentation of bipolar II disorder

BDII is a distinct disorder from BDI, with a similar Canadian prevalence (0.67% compared to 0.87% for BDI).[7] The diagnosis of BDII requires one or more episodes of hypomania, one or more episodes of depression, and an absence of manic episodes. The DSM-5 criteria for hypomania are similar to those for mania, with symptoms being uncharacteristic of the individual, observable by others, and lasting at least 4 consecutive days. In contrast to mania, they cannot be severe enough to cause marked impairment or require hospitalization, and there must be an absence of psychosis. Further, DSM-5 has added a mixed feature specifier to hypomania as well. The diagnosis of BDII is generally stable over time, although there may be a higher risk of conversion to BDI early in the illness, suggesting that BDII may be a risk factor or prodrome of BDI in some patients.[423]

Why is lithium recommended as a second-line agent for bipolar II depression?

Reconciling conflicting data

In a 16-week double blind RCT, lithium was as effective as sertraline and lithium + sertraline combination (427) which qualifies lithium for Level 2 evidence. Additional supporting data come from a single-blinded trial which showed that lithium was as effective as lamotrigine in treating BDII depression over 6 weeks (445). However, neither of these studies had a placebo arm. Positive placebo-controlled data come from 4 small placebo-controlled crossover studies conducted in the 1960s and 1970s, in which lithium was effective in a mixed sample of BDI and BDII depressed patients (446-449). Results were reported separately for BDII in 2 of the studies and were identical to BDI (pooled response rate = 65% for both) (446).

In contrast, in the only modern a placebo-controlled parallel group study, lithium was not superior to placebo in BDII depression (254). Further, lithium was less effective than venlafaxine in a 12-week RCT (450).

A potential explanation might have to do with trough serum lithium levels. Lithium levels ranged from 0.8-1.3 mEq/L, and were often at the high end of that range in the older placebo-controlled RCTs while in the negative placebo-controlled RCT, the mean serum lithium level was lower (<0.61 mEq/L in the combined BDI + BDII sample, not reported separately for BDII). Thus, the optimal serum level for treating bipolar II depression is unclear. However, based on the placebo-controlled BDII trials, as well as placebo-controlled studies in BDI (247), a serum level of 0.8-1.2 mEq/L appears most likely to be beneficial.

In addition to the evidence for efficacy in acute depression, lithium also has efficacy in preventing mood episodes in BDII (400, 452-454). Therefore, in balance, we believe the evidence, though mixed, justifies recommending lithium as a second-line agent for BDII depression.

FIGURE 5 Lithium as a second-line agent for bipolar II depression: Summary of evidence.
BDI, bipolar disorder type I; BDII, bipolar disorder type II; BDNOS, bipolar disorder not otherwise specified; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Should antidepressants be used in bipolar II depression?

Addressing the controversy

The question of whether, and if so when and how, to use antidepressants in BDII remains controversial due to concerns regarding both safety (particularly the possibility of hypomanic switch, mixed symptoms, and increased cycling) and efficacy.

With respect to safety, a meta-analysis that compared rates of antidepressant-associated mood elevations in BDII, BDI, and MDD reported that they were significantly less frequent in BDII than BDI, and occurred almost exclusively into hypomania rather than mania (454). Switch rates were low even during antidepressant monotherapy and with antidepressants associated with high switch rates in BDI (tricyclics, venlafaxine). An ISBD task force report on antidepressants also concluded that their risk-benefit ratio was more favorable in BDII (261, 449).

The issue of efficacy is less clear due to limited evidence. RCTs have shown that sertraline monotherapy was as effective as lithium and lithium+ sertraline combination, and that venlafaxine monotherapy was more effective than lithium, sufficient for level 2 evidence for these agents. In a RCT of BDI and BDII patients, bupropion was shown to be as effective as sertraline and venlafaxine (277). Open-label data also suggest efficacy for fluoxetine, and there are maintenance data for venlafaxine and fluoxetine in preventing relapses. These positive findings should be balanced against the fact that paroxetine and bupropion were not better than placebo for acute depression in patients taking concomitant mood stabilizing medications. Moreover, it is important to bear in mind that 1) there are no placebo-controlled acute-phase trials of antidepressant monotherapy in BDII, 2) many antidepressants have not been studied at all (and we do not believe it is warranted to extend positive findings from sertraline/venlafaxine -or for that matter negative findings from paroxetine/bupropion -to "antidepressants" generally), 3) the existing trials enrolled people with pure (non-mixed) depression, and their efficacy/safety in the broader spectrum of BDII patients is unclear, and 4) many of the existing trials have significant weaknesses, including one or more of: low dosing of the antidepressant; sub-therapeutic dosing of comparator medications; and lack of replication.

All of this makes it particularly difficult to make evidence based recommendations regarding antidepressants in BDII. We have restricted our recommendations to the specific agents that have been studied, and we recommend bupropion, sertraline,and venlafaxine monotherapy as second-line treatments; and fluoxetine as third-line. We further recommend that any antidepressant, especially in monotherapy, be reserved for patients with pure depression and avoided in those with mixed symptoms or a history of antidepressant-induced hypomania (261). Whether antidepressants should also be avoided in patients with rapid cycling is unclear, since some studies report poorer outcomes in rapid-cycling patients (455) while others do not (450, 456-458). Patients prescribed antidepressants must be educated regarding early-warning signs of hypomania and carefully monitored for them. Finally, there is a pressing need for further studies of other antidepressants in BDII, in both monotherapy and combination therapy.

FIGURE 6 Antidepressants for bipolar II depression: What is their role?
BDI, bipolar disorder type I; BDII, bipolar disorder type II; ISBD, International Society for Bipolar Disorders; MDD, major depressive disorder; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Although hypomania is, by definition, less severe than mania, the disability associated with BDII is comparable to that associated with BDI,[14,424] and the economic burden of BDII is up to four times greater.[425,426] This is because patients with BDII spend as much time symptomatic as those with BDI, with mood symptoms predominantly in the depressive phase.[427,428] Rates of attempted and completed

Why is lamotrigine a second-line recommendation for bipolar II depression?
Reconciling conflicting data

Lamotrigine monotherapy was studied in two trials in BDII depression: one in which 221 BDII patients received 200 mg/day or placebo for 8 weeks, and a second in which 206 BDI or BDII patients (N = 84 with BDII) received 100–400 mg/day for 10 weeks (254). Both produced negative results. A meta-analysis confirmed that lamotrigine was not superior to placebo in BDII depression, although it did separate from placebo in BDI (248). Several methodological shortcomings likely resulted in the studies underestimating the drug's effect, including 1) a slow titration which resulted in subjects being on the target dose for a short time, 2) a target dose lower than that often used in clinical practice and in successful maintenance studies (255, 324), and 3) higher placebo response rates. In contrast, a single-blind RCT with a relatively high dose (final peak dose=300mg) and a longer duration (16 weeks) found that lamotrigine monotherapy was as effective as adequately-dosed lithium (mean final serum level=1.1 mEq/L) in N=98 BDII patients (445). Two large RCTs in BDI+BDII and a 12-week open-label trial in patients with BDI+BDII+BDNOS also reported that adjunctive lamotrigine was effective, but did not report results separately for BDII (252, 253). Finally, lamotrigine has robust efficacy in preventing depressive relapse in BDI and BDII (324, 459). Taking all of these factors into consideration we recommend lamotrigine as a second-line treatment, particularly for patients who can tolerate a slow titration and delayed effect.

FIGURE 7 Lamotrigine as a second-line agent for bipolar II depression: Summary of evidence
BDI, bipolar disorder type I; BDII, bipolar disorder type II; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

suicide are similar in BDI and BDII, with approximately one-third of patients with BDII attempting suicide over the course of their illnesses[429] and one in twenty-five completing suicide.[430]

6.2 | Pharmacological treatment of bipolar II disorder

6.2.1 | General considerations for interpreting recommendations

The treatment of BDII has been understudied relative to BDI. This is probably due to the long-standing but discredited impression of BDII as a less severe form of BD. The number of RCTs in BDII is substantially smaller than that in BDI, and those studies that do exist are frequently under-powered. It also remains common for trials to enrol patients with both BDII and BDI without reporting results separately, making it difficult to determine if there are clinically meaningful differences in treatment response between the two illnesses. This is important because, while clinical experience and the results of many studies suggest that response to mood stabilizers and antipsychotics is similar in BDII and BDI, there are enough exceptions to suggest this should not be taken for granted.[248,405,431] This is also the case for antidepressants, which may have a more favourable risk-benefit ratio in BDII (reviewed below). Therefore, in formulating our recommendations, studies that enrolled patients with both BDII and BDI but did not report results for BDII separately are assigned level 4 status (expert opinion) if the proportion of patients with BDII was less than 50%.

The relative paucity of large, methodologically sound clinical trials in BDII creates challenges in formulating evidence-based guidelines. As will be seen, there are fewer treatments with high-quality evidence in BDII compared to BDI and fewer first-line treatment recommendations. The limitations of the evidence base necessitate an awareness of the nuances of the available studies, and a greater reliance on clinical experience. We thus have endeavoured to be clear in outlining the rationale for selecting first, second, and third-line treatments for hypomania, depression, and maintenance treatment of this important illness. There is clearly a pressing need for adequately powered trials in BDII across all illness phases.

TABLE 20 Strength of evidence and treatment recommendations for maintenance treatment of bipolar II disorder

Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone[a]	Level 4

[a]Primarily for prevention of hypomania.

6.2.2 | Acute management of hypomania

The general principles for assessing mania apply to hypomania. For some patients, hypomania causes no to minimal functional impairment and may even be associated with brief periods of above-normal functioning. However, prolonged, relatively severe, or mixed or irritable hypomania may be impairing.[423] Treatment should include discontinuing agents that can worsen or prolong symptoms, including antidepressants and stimulants, and initiating appropriate pharmacotherapy.

Unfortunately, many standard medications for mania, including lithium and most atypical antipsychotics, have not been studied in hypomania. There are four placebo-controlled trials that investigated divalproex (level 4),[432] *N*-acetylcysteine (level 4),[433] and quetiapine (level 4)[434,435]; and one open-label study of risperidone (level 4)[436] in acute hypomania. The studies generally suggested efficacy but all had significant weaknesses, including one or more of: (i) small sample sizes, (ii) mixed samples with BDI, BDII, and BD NOS; (iii) mixed samples with hypomania and mania, and (iv) positive findings on some but not all outcomes. The small numbers of patients and mixed samples mean

that even the placebo-controlled trials only met criteria for level 4 evidence (Table 1).

These methodological limitations, coupled with the lack of clinical trial evidence for many medications, make it difficult to make specific suggestions for the treatment of hypomania. Clinical experience suggests that all anti-manic medications are also efficacious in hypomania. Thus, when hypomania is frequent, severe, or impairing enough to require treatment, clinicians should consider mood stabilizers such as lithium or divalproex and/or atypical antipsychotics. *N*-acetylcysteine may also be of benefit, but further studies are needed.

6.2.3 | Acute management of bipolar II depression

The general principles for assessing depression in patients with BDI apply to those with BDII. First, second, and third-line treatment options are listed below and shown in Table 19. Specific considerations regarding each treatment are highlighted in the relevant sections.

First-line

Quetiapine is the only recommended first-line treatment for BDII depression (level 1). Pooled analyses of five identically designed trials demonstrated that quetiapine was superior to placebo, and moreover was equally effective for acute depression in BDI and BDII.[243,437] The latter finding must be reconciled with the fact that quetiapine beat placebo in only three of the five individual trials in patients with BDII, compared to all five in patients with BDI.[253,290,438-440] This is probably because the smaller sample of BDII patients—only about half as many patients with BDII as BDI were enrolled in each of the trials—provided less statistical power for BDII. Finally, open-label studies also suggest efficacy for adjunctive quetiapine (level 4).[441,442]

Second-line

Second-line treatments include lithium, ideally at a serum level of 0.8-1.2 mEq/L (level 2) (Figure 5), and the antidepressants sertraline (level 2) [426] and venlafaxine (level 2),[443,444] mainly for patients with pure (non-mixed) depression (Figure 6). Lamotrigine (level 2) is also recommended as a second-line agent despite conflicting evidence, with the rationale for this provided in Figure 7. ECT (level 3)[261] can also be considered second-line and is a good option, particularly for treatment refractory patients and those in need of rapid response.

Third-line

The third-line options include monotherapy with divalproex (level 4)[258,459,461,462-466] fluoxetine (mainly for patients with pure depression) (level 3)[467-469] tranylcypromine (level 3),[278] or ziprasidone (solely for patients with depression and mixed hypomania) (level 3).[470,471] Adjunctive agomelatine (level 4),[472] bupropion (level 4)[276] eicosapentaenoic acid (EPA) (level 4),[473-475] *N*-acetylcysteine (level 4),[476] pramipexole (level 3),[274] or thyroid hormones (level 4)[272] may also be considered.

Intravenous ketamine (level 3)[477,478] has rapid onset of efficacy and may be considered for patients who are refractory to first and second-line treatments, as well as for those in need of rapid response.

No specific recommendation/agents that require further study

A number of agents do not have sufficient data to warrant specific recommendations for BDII depression, including cranial electrotherapy stimulation (CES),[479] dextromethorphan + quinidine,[480] light therapy,[481-485] lisdexamfetamine (adjunctive),[300] olanzapine,[486] pioglitazone,[302] adjunctive pregnenolone,[306] celecoxib,[297] levetiracetam,[487] adjunctive lisdexamfetamine,[300] s-adenosylmethionine,[488-490] acetyl-L-carnitine + alpha-lipoic acid,[491] adjunctive modafinil,[268] rTMS,[275,492,493] and memantine.[494]

Not recommended

Based on negative placebo-controlled data, we do not recommend paroxetine (level 2 negative).[245]

6.2.4 | Maintenance treatment

Maintenance treatment is important to prevent relapse, reduce subsyndromal symptoms, and improve quality of life. As with BDI, selection of an agent should be informed by acute phase treatment. Recommended agents and their evidence ratings are listed in Table 20.

First-line

Monotherapy with quetiapine (level 1),[495] lithium (level 2),[399,450,452] and lamotrigine (level 2)[323] are first-line options.

Quetiapine. In two 52-week maintenance studies, patients with BDII who achieved remission from depression with quetiapine monotherapy continued it or switched to placebo.[495] A pooled analysis reported that patients treated with quetiapine had a significantly longer time to relapse into any mood episode (hazard ratio [HR] 0.33, or a 67% reduction in the risk of relapse) and into depression (HR 0.28 or a 72% risk reduction). Time to relapse into hypomania was not significantly greater (HR 0.65 or a 35% risk reduction). The latter finding may be related to the low base rate of hypomania, which occurred in only 10% of all study participants. Quetiapine was at least as effective in BDII as in BDI, for which the risk reductions were 42% for any relapse, 48% for depression, and 30% for mania. Adjunctive quetiapine was also studied in a 6-month single-blind trial which randomly assigned patients with either BDI or BDII to lithium or quetiapine added to treatment as usual. They were equally effective in preventing relapse.[453] Results were not presented separately for BDII, but BDII patients responded better to both treatments than did BDI patients.

Lithium. In three placebo-controlled RCTs conducted in the 1970s and 1980s (duration = 11-25 months), lithium decreased the frequency and/or severity of hypomanic and depressive episodes.[399,450,452] Serum lithium levels were 0.8-1.2 mEq/L. A number of active comparator studies also support lithium. As noted above, lithium was as effective as quetiapine in preventing relapse in a 6-month single-blind trial.[453] A 20-month study comparing lithium and divalproex in rapid cycling BDI

+ BDII found the two drugs to be equally effective in preventing relapses.[496] The authors noted that findings were similar for BDII and BDI, but results were otherwise not reported separately for BDII. In a 2.5-year study in BDII + BD NOS, lithium and carbamazepine were equally effective on most outcomes, although a numerical advantage favoured carbamazepine for reducing clinical plus subclinical recurrence.[405] In contrast, head-to-head comparisons with antidepressants (reviewed below) found that lithium was not as effective in preventing depressive relapse as fluoxetine or venlafaxine.[469,497] This may be explained by the mean lithium levels, which were 0.7 mEq/L in both studies, while the fluoxetine trial was also enriched for fluoxetine responders.

Long-term naturalistic data also provide strong support for lithium. In a 6-year study of patients with either BDI or BDII (39% with BDII), lithium reduced time in hypomania/mania by 61% and time in depression by 53% in the entire sample, compared with the period before lithium treatment was initiated.[498] The authors noted that the proportion of time with mood symptoms was significantly lower for BDII than for BDI.

Lamotrigine. In a 6-month placebo-controlled RCT of lamotrigine monotherapy in rapid cycling BDI + BDII, post hoc analysis showed that significantly more lamotrigine-treated than placebo-treated patients with BDII were stable without recurrence into any mood episode,[323] although lamotrigine was not superior to placebo in BDI. In a large 52-week RCT in BDI + BDII, adjunctive lamotrigine was superior to placebo for improving depression severity and remission rates. However, results were not presented separately for BDII.[251] Open-label trials and retrospective chart reviews also support lamotrigine.[248,499-502]

Second-line

Monotherapy with venlafaxine (level 2) or fluoxetine (level 3) are second-line options.

Venlafaxine. In a small 6-month RCT in patients with BDII who responded acutely to venlafaxine or lithium without hypomanic switch, there was a trend for lower rates of relapse into depression for patients treated with venlafaxine. Further, the rate of sustained response was significantly greater in those who continued venlafaxine compared to those who continued lithium.[497] No hypomanic episodes occurred in either group.

Fluoxetine. In a 50-week RCT, the mean time to relapse into depression was significantly longer for fluoxetine than for lithium or placebo. Patients had responded acutely to open-label fluoxetine, making the sample enriched for fluoxetine response. Hypomanic episodes occurred in a similarly low frequency in the three groups.[469] In a separate small 6-month placebo-controlled trial, there was a statistical trend for lower relapse rates with fluoxetine compared to placebo.[503] Finally, a post hoc analysis of a large 12-month placebo-controlled trial found that response rates to fluoxetine were similar in BDII and MDD.[468] However, it did not report whether fluoxetine was superior to placebo in BDII.

Third-line

Divalproex (level 4),[504] carbamazepine (level 3),[405] escitalopram (level 3),[505] other antidepressants (level 3),[454] and risperidone (mainly for prevention of hypomania) (level 4)[436] may be considered as third-line options.

No specific recommendation/agents that require further study

There are insufficient data to make a recommendation regarding olanzapine.[506]

7 | SPECIFIC POPULATIONS

7.1 | Management of bipolar disorder in women at various stages of the reproductive cycle

7.1.1 | Pre-conception, psychoeducation and contraceptive counselling

The importance of pre-conception counselling should be raised with all women of child bearing age. It should be provided for all patients at least 3 months prior to considering pregnancy or immediately for those already pregnant. The issues most frequently raised are fear of adverse

TABLE 21 US Food and Drug Administration (FDA) classification of teratogenicity for medications commonly used in bipolar disorder[a]

	Pregnancy risk category[b]	Lactation risk category[c]
Lithium	D	L4
Anticonvulsants		
Carbamazepine	D_m	L2
Divalproex	D_m	L4
Lamotrigine	C_m	L2
Atypical antipsychotics		
Aripiprazole	C_m	L3
Clozapine	B_m	L3
Olanzapine	C_m	L2
Quetiapine	C_m	L2
Risperidone	C_m	L2
Ziprasidone	C_m	L2
SSRI antidepressants		
Citalopram	C_m	L2
Escitalopram	C_m	L2
Fluoxetine	C_m	L2
Fluvoxamine	C_m	L2
Paroxetine	D_m	L2
Sertraline	C_m	L2
Other antidepressants		
Bupropion	B_m	L3

[a]FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final Rule (PLLR). SEE TEXT FOR DETAILS.
[b]Adapted from ACOG Committee on Practice Bulletins–Obstetrics[878]: US Food and Drug Administration Rating. A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out (human data lacking, animal studies positive or not done); D = positive evidence of risk (benefit may outweigh risk). The "m" subscript is for data taken from the manufacturer's package insert.
[c]Hale TW and Rowe HE.[879] Lactation risk categories are listed as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated.

effects of medications on the fetus, fear of illness recurrence, and genetic transmission to offspring.[507] Other important topics to review include the effect of BD on risk for gestational hypertension, antepartum haemorrhage, induction of labour, caesarean section, instrumental delivery, preterm delivery, and neonatal size.[508,509] Discussion of modifiable risk factors is critical in pre-conception management of BD. For instance, pregnant women with BD are more often overweight, more often smoke tobacco during pregnancy, have poorer diet quality, and present more often with a history of drug and alcohol misuse in pregnancy.[509] Modification of these risk factors may have a significant positive impact on outcomes for both the mother and child.

Decisions should be made collaboratively on whether medications should be continued, discontinued, or switched; and whether any dosage changes are needed. Conventional antipsychotics and risperidone may need to be discontinued to increase the likelihood of conception, as these medications often increase serum prolactin levels and thus interfere with ovulation and decrease fertility.[510] For women who wish to have a medication-free pregnancy, it might be appropriate to have one or more psychotropic medications gradually tapered off prior to conception provided they have been clinically stable for a minimum of 4-6 months and are considered at low risk of relapse. Information regarding potential teratogenic effects of different psychotropic medications, as well as limitations of the scientific evidence, should be discussed and carefully considered. The decision to stop medications pre-conceptually should ideally occur only after careful individualized risk-benefit analysis for a given patient.[511-513] If pharmacotherapy is required, monotherapy at minimum effective dose is recommended whenever possible.[514,515]

Contraceptive counselling, including emphasis on its effectiveness in reducing the likelihood of unintended pregnancies, should be included as part of a comprehensive treatment plan for women with BD.

Several anticonvulsants, including carbamazepine, topiramate, and lamotrigine, can affect the pharmacokinetics of oral contraceptives and some might significantly reduce the effectiveness of oral contraceptives, and this should be considered when making treatment decisions.[516,517] Oral contraceptives might also have effects on the efficacy of lamotrigine via reduction in lamotrigine levels.[516]

While folic acid supplementation is protective against spontaneous spina bifida, there is not enough evidence to indicate that folic acid, even in high doses, protects against spina bifida following the use of anticonvulsants.[518] In addition, Health Canada recommends that "Valproate products (valproic acid, divalproex sodium) should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate." Health Canada also recommends that women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of valproate products during pregnancy, and in women planning to become pregnant every effort should be made to switch to appropriate alternative treatment prior to conception.[519]

Regardless of treatment decisions made prior to or following conception, it is also important to work with the patient to develop and agree upon a monitoring schedule and treatment plan to be implemented should clinically significant symptoms emerge. Education about the risks of psychotropic medications is critical, and careful discussion is needed regarding the magnitude of risks and benefits and limitations with the data. It is important to acknowledge the patient's desire to do what is right for the child and support the decision made. Whenever appropriate, involve partners in the discussion and review the decision and supporting evidence for it directly or through educational materials.[520]

7.1.2 | Screening for bipolar disorder during pregnancy and postpartum

All women with depressive symptoms should be screened for BD during pregnancy and the postpartum period.[521,522] Standardized screening tools such as the Mood Disorder Questionnaire alone or in conjunction with the Edinburgh Postnatal Depression Scale are useful.[521-524] Importantly, screening should be followed by a clinical interview to confirm or exclude a diagnosis of BD. Women should also be assessed for other psychiatric disorders that commonly co-occur with BD, such as anxiety disorders or obsessive compulsive disorder (OCD).[525]

7.1.3 | Pharmacological management of bipolar disorder during pregnancy

Given the complexity of the risks faced by women with BD in pregnancy and puerperium, it is good clinical practice to encourage liaison between the mental health and obstetrics/gynecology teams. A longitudinal study conducted in a tertiary care centre found a high risk of recurrence during pregnancy: 85% of pregnant women with BD who discontinued a mood stabilizer and 37% of those who were maintained on one or more mood stabilizers experienced a mood episode—predominately depressive or mixed—during pregnancy. For nearly half of the patients, recurrence occurred in the first trimester, with the median time for recurrence for those abruptly discontinuing treatment being 2 weeks, compared to 22 weeks for those who were gradually tapered off.[511] However, studies from primary care, as well as obstetric centres, found low rates of relapse or hospitalizations in pregnancy.[526]

The hierarchies presented throughout these guidelines should be followed for management of the various phases of BD, with consideration given to specific risks associated with the use of each medication using the most up-to-date information available from the US Food and Drug Administration (FDA) website (http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm117976.htm).

Table 21 includes a brief overview of medications commonly used in BD and the risk categories. This list should not be viewed as complete or comprehensive. Further, the FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final

Rule (PLLR) with narrative sections and subsections. For instance, for pregnancy, the information for each medication is provided using the following subheadings: Pregnancy exposure registry, Risk summary, Clinical considerations, and Data. The last three subsections apply to medication risks during lactation. The FDA has not finalized and published the data for all medications as of completion date of these guidelines (February 2018), and new data appear to suggest that risks may have been overestimated for some medications such as lithium.[527] Thus clinicians are strongly advised to use all the current data, including the FDA PLLR information if available, in collaboration with patient and family members to make final treatment decisions.

Wherever possible, psychosocial strategies should be preferred over medications in the first trimester as this period holds the highest risk for teratogenicity. When medications are deemed necessary, preference should be given to monotherapy using the lowest effective dose.

Each pregnancy should be closely monitored and appropriate screening tests (eg, foetal ultrasound if lithium is used in the first trimester) should be performed.[528] Divalproex should be avoided during pregnancy due to elevated risk of neural tube defects (up to 5%), even higher incidences of other congenital abnormalities, and evidence of striking degrees of neurodevelopmental delay in children at 3 years of age and loss of an average of nine IQ points.[529-531] Because of changes in physiology in the second and early third trimesters, such as increased plasma volume, hepatic activity, and renal clearance, patients may require higher doses of medications towards the later part of the pregnancy. Prenatal vitamins, including high-dose (5 mg/day) folic acid, are also recommended, preferably even before conception and continuously through pregnancy; and preparations containing choline have recently been recommended as possibly preventive of the later development of schizophrenia.[532] While it is important to note that folic acid may reduce the effectiveness of lamotrigine,[251] the anti-teratogenic effects of folate may outweigh the potential for this loss of effectiveness. However, recent concerns have been raised regarding a potential association between very high plasma levels of maternal folate and risk of autism spectrum disorders.[533]

7.1.4 | Pharmacological management of bipolar disorder during the postpartum period

The postpartum period is a time of elevated risk for recurrence, with 66% of women who were medication free during pregnancy and 23% of those on treatment experiencing a mood episode following the delivery.[534] The risk of postpartum relapse is highest in women who also experienced a mood episode during pregnancy and those who are not on prophylactic treatment.[535] Despite the high prevalence of postpartum episodes, there is a dearth of studies investigating the efficacy of medications during this period. There is evidence of efficacy of benzodiazepines, antipsychotics, and lithium for postpartum mania,[535] and quetiapine for postpartum bipolar depression (level 4).[536] There are no studies of psychotherapy in the acute or preventative treatment of bipolar postpartum depression.[537]

Patients should be encouraged to initiate or optimize maintenance treatment as soon after giving birth as possible, with preference given to medications that have previously been shown to be successful. Near delivery, close monitoring is essential for early detection and management of symptoms that might signal onset of a mood or psychotic episode.[538] If an acute mood episode emerges in the postpartum period, the hierarchies for non-postpartum episodes should be followed, but, because most psychotropic medications are excreted in breast milk, treatment choice should take into consideration safety in breastfeeding when applicable.

The FDA website mentioned in the previous section as well as Table 21 also include information on lactation. The FDA PLLR should be consulted for further information about medication risks, as many are secreted in milk, if breastfeeding is being considered.

The potential risks and benefits of taking medications while breastfeeding should be discussed with the patient. Education about early recognition of drug toxicity and requirement for ongoing monitoring of infants is also critical.[539] A recent systematic review suggested quetiapine and olanzapine as preferred choices for breastfeeding, considering their relatively lower infant dosages.[540] The impact of medication on the infant can be reduced by scheduling medication administration after breastfeeding.[541]

Replacing or supplementing breast milk with formula can also be considered. Although there are many benefits to breastfeeding, associated sleep disruption may increase the risk of mood episodes in women with BD. If possible, bottle feeding at night by the woman's partner or a support can be beneficial to allow the woman to maintain a better sleeping schedule. In women with postpartum psychosis or mania, breastfeeding may be more risky, and therefore may not be indicated, as the mother may be too disorganized to safely breastfeed.[542]

As childbirth can be a trigger for first onset of hypomania/mania in women with MDD, antidepressants should be used cautiously, especially in women with a family history of BD.[543] Women with first onset of depression in the postpartum period or those who have recurrence of depression during the early postpartum period, may also be at a high risk of switching to BD following treatment with antidepressants.[537]

7.1.5 | Impact of the menstrual cycle on symptoms

Despite the paucity of large, well-designed research studies examining the impact of the menstrual cycle on mood symptoms in BD, accumulating evidence suggests that hormonal changes can impact the course of illness. Several case reports and prospective studies suggest that women who experience premenstrual symptom exacerbation are more likely to have a highly symptomatic and relapse prone illness.[544,545] One of the largest studies (n = 1099) found that women who met DSM-5 provisional criteria for premenstrual dysphoric disorder (PMDD) had an earlier illness onset, more comorbid Axis I disorders, a higher number of hypomanic/manic and depressive episodes, and higher rates of rapid cycling.[546] In this study, there was a closer gap between BD onset and age of menarche in women with comorbid PMDD, which suggests that sensitivity to endogenous hormones may influence the onset and the clinical

TABLE 22 Differential diagnosis of manic symptoms in children and adolescents

Symptom	Bipolar mania hypomania	Attention deficit hyperactivity disorder	Oppositional defiant disorder
Elation	Episodic, prolonged, pathological (inappropriate to context or uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
Irritability	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (eg, ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
Sleep	Reduced need for sleep (ie, significantly less sleep than usual without increased daytime fatigue or somnolence); change must be mood-related	Insomnia (ie, difficulty falling asleep); can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic; may defy bedtime rules or routine
Grandiosity	Distinct uncharacteristic increase in confidence or self-importance; change must be mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common but not necessarily mood-related
Hyperactivity and distractibility	Episodic; if comorbid ADHD is diagnosed, then distinctly "worse than usual" change must be mood-related	Diagnostic criteria, nonepisodic	Not prominent or episodic

ADHD, attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder (Adapted from Goldstein and Birmaher 2012[555]).

course of BD. Premenstrual syndrome (PMS) and PMDD also occur more frequently in women with BD.[547,548] Importantly, an accurate diagnosis of comorbid PMDD in women with BD is made during euthymia, with a minimum of 2 months of prospective symptom charting.[549]

7.1.6 | Menopause

For many women, stress and hormonal changes associated with the transition to menopause may increase or trigger mood symptoms.[550-552] A post hoc analysis of the prospective Systematic Treatment Enhancement Program for Bipolar disorder (STEP-BD) study showed increased rates of depressive, but not manic episodes during menopause transition.[553] However, due to the paucity of clinical trials in this area, more data are needed before treatment recommendations can be made.[554]

7.2 | Management of bipolar disorder in children and adolescents

7.2.1 | Presentation and diagnosis

As the following section comprises only a brief overview of the epidemiology, phenomenology, and differential diagnosis of BD in children and adolescents, the reader is referred to more detailed reviews for further information.[555-560]

Between one-third (community samples) and two-thirds (clinical samples) of patients with BD experience their first mood episode during childhood or adolescence, with an earlier onset related to a more severe illness characterized by increased symptom burden and comorbidity.[561,562] In contrast to the controversies of as recently as a decade ago, there is now far greater consensus in the field that, although there are developmental differences in the manner in which symptoms manifest themselves, the actual diagnosis of BD in children and adolescents should be made based on the same set of symptoms as applied to adults.[563] When defined rigorously according to DSM-5 criteria, the course of illness in childhood and adolescence is characterized by eventual high rates of symptomatic recovery, but also high rates of recurrence, even in the context of naturalistic treatment.[564] While the concepts of "over-diagnosis" and "over-treatment" in pediatric BD have received substantial attention,[565] representative population studies demonstrate that adolescent BD is characterized by low rates of treatment, alongside high rates of suicidality and comorbidity.[566,567] Risks of incorrectly diagnosing and treating BD in a child or adolescent should thus be carefully weighed against the risk of incorrectly or not diagnosing or treating,[568] keeping in mind that the duration of treatment delay has been shown to be an independent risk factor for a poor outcome in adulthood.[569]

Distinguishing early-onset mania or hypomania from other psychiatric disorders is important as there is a high level of symptomatic overlap for multiple conditions including but not limited to ADHD, oppositional defiant disorder (ODD), disruptive mood dysregulation disorder (DMDD), substance abuse, personality disorders and generalized anxiety disorder[555,570] (Table 22). The discrete episodes of mania/hypomania and the non-overlapping symptoms can facilitate accurate diagnosis. When a comorbidity is present, such as ADHD, overlapping symptoms (eg, distractibility and hyperactivity) should only count towards a diagnosis of mania or hypomania if they intensify during intervals of elation or irritability. Notably, ADHD is an ongoing condition whereas BD is episodic, and decreased sleep, hypersexuality, hallucinations or delusions, and homicidal or suicidal thoughts and actions occur with childhood mania, but are rare or absent in uncomplicated ADHD.

It is important to note that, while chronic irritability with episodic behavioural outbursts or rages can be seen in multiple paediatric psychiatric disorders (including emerging personality disorders, substance abuse,

Reconciling the paucity of RCT data with abundant clinical experience in determining level of recommendation for treatment of pediatric bipolar depression

Aside from lurasidone, which has positive RCT data (597) alongside good tolerability, options include either treatments with substantial tolerability concerns (olanzapine-fluoxetine combination) or treatments with no RCT data (eg. lithium, lamotrigine) or without positive RCT data (eg.quetiapine). In this instance, clinical experience combined with tolerability considerations and adult data informed the ranking of recommendations. Lithium and lamotrigine have not been tested in RCTs in pediatric bipolar depression. However, there is abundant clinical experience with these agents in treating depression in the pediatric group alongside positive open trials. Further, these agents are recommended for treating acute bipolar in adult populations, and they have good tolerability. Thus, despite lack of RCT data, they are recommended as second-line agents for treating acute bipolar depression in pediatric population.

In terms of quetiapine, of the two negative RCTs (601, 602), one had a dose range of 300-600 mg/day but was limited to 32 participants and had a 67% placebo response rate. The other study was dosed at only 150-300 mg/day and had a 55% placebo response rate. One can argue that the quetiapine studies have been failed, rather than truly negative, studies. Therefore, given its demonstrated efficacy in adult bipolar depression and methodological problems in studies of pediatric bipolar depression and based on clinical experience, it is recommended as a third-line option.

Ultimately, treatment decisions in general, but particularly in the context of empirical uncertainty, should be informed by a thorough discussion of comparative risks and benefits of competing options. Risk-benefit ratios may differ across patients depending on factors such as BD subtype, comorbid anxiety, and sleep disturbance.

FIGURE 8 Treatments for pediatric bipolar depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

ODD, pervasive developmental disorders, and major depressive episodes), such irritability and explosiveness are not sufficient to make a diagnosis, even when severe. The recent DSM-5 diagnosis DMDD—which includes chronic irritability as a defining feature—lists BD as an exclusion criterion. However, the DMDD phenotype is evident in about 25% of adolescents with episodic BD, and is associated with factors such as greater family conflict and ADHD comorbidity.[571] Classical BD and chronic irritability are therefore not mutually exclusive, the nonspecific nature of the latter notwithstanding.

A significant minority of children or youth with MDD will eventually go on to develop BD, with an average rate of 28% being reported.[572,573] Risk factors for switch to mania following a depressive episode include a family history of mood disorders, emotional and behavioural dysregulation, subthreshold manic symptoms, cyclothymia, atypical depression and psychosis.[572] A recent meta-analysis suggested that the most potent predictors were family history, an earlier age of onset and the presence of psychotic symptoms.[574] There is an increased prevalence of BD among offspring of parents with BD.[575-577] Although there is no uniform strategy for managing depression (or ADHD, anxiety, etc.) in the child of a parent with BD, increased caution is warranted when prescribing antidepressant or stimulant medications as these have the potential to precipitate mania/hypomania.[578] Patients and their parents should be informed of the potential switch risk and close monitoring for treatment-emergent manic/hypomanic switch should be instituted.

Self-report and/or parent-reported questionnaires can be informative and can raise the index of suspicion for BD.[579] However, scores on such questionnaires as the Child Behaviour Checklist (CBCL) "dysregulation phenotype", previously described as "BD phenotype", have poor capacity for differentiating BD from other complex and severe symptomatic presentations.[580] Questionnaires can be used as screeners, but do not substitute for a thorough diagnostic evaluation. Longitudinal rating by parents may be most helpful in diagnosis and assessment of treatment response. An online program for weekly parental ratings (of depression, anxiety, ADHD, oppositional behaviour, and mania) of children aged 2-12 years is available at www.bipolarnews.org, click on Child Network.[581]

7.2.2 | Pharmacological management

General principles

The general principles for managing adults with BD also apply to children and youth. In youth, themes of comorbidity and tolerability are accentuated. Comorbid ADHD is more common in children and adolescents as compared to adults with BD. Moreover, ADHD symptoms often do not improve following mood stabilization, and may require concurrent ADHD treatment. In addition, due to elevated risk for accelerated atherosclerosis and early cardiovascular disease in this population, cardiovascular risk factors should also be assessed regularly and intervention implemented. Lifestyle management including attention to diet, substance use, smoking and physical activity should be implemented alongside any psychological or pharmacological interventions.[582] Relatedly, children and adolescents are more susceptible than adults to the metabolic side effects of psychiatric medications, particularly the atypical antipsychotics that are considered first-line treatments.[583] Taken together, these distinguishing features underscore the importance of ensuring that polypharmacy, as often required, is judicious and informed by a balance of factors including mood symptom burden, global functioning, and physical health.

Acute management of mania

First-line. Lithium (level 1),[583-585] risperidone (level 1),[584,586] aripiprazole (level 2),[587] asenapine (level 2),[588] and quetiapine (level 2)[583,589] are recommended as first-line options. Risperidone may be preferable to lithium for non-obese youth, and youth with ADHD.[584]

Second-line. Due to safety and tolerability concerns, olanzapine (level 2)[590] and ziprasidone (level 2)[591] should be considered second-line options. Quetiapine adjunctive therapy (level 3)[592] is also recommended as a second-line treatment.

Third-line. Despite low response rates in two RCTs, a long history of use among adults with BD, combined with positive findings in open-label studies are grounds for considering divalproex as a third-line option for youth who do not respond to or tolerate first or second-line agents (level 4).[593]

Not recommended. Oxcarbazepine was not superior to placebo in a large RCT (level 2 negative).[594]

Acute management of bipolar depression

The data in paediatric samples are very limited, and complicated by extremely high placebo-response rates in RCTs. These recommendations are therefore to a greater extent informed by clinical experience and studies in adults than the above acute mania recommendations (see Figure 8).

First-line. A recently published RCT found that lurasidone was superior to placebo (level 2)[595] in improving depressive symptoms in children and adolescents with acute bipolar depression; however there is comparatively little clinical experience in this population. Nevertheless, given its efficacy and clinical experience in adult bipolar depression, lurasidone is recommended as a first-line treatment.

Second-line. Although lithium and lamotrigine were recommended as first-line agents for bipolar depression in adults, there are only open-label data for lithium (level 4)[596] and lamotrigine (level 4)[597] in children and youth. Despite limited RCT data, there is, however, substantial clinical experience with these agents as they are widely used in clinical practice. For this reason, together with the strength of evidence in adults, lithium and lamotrigine are recommended as second-line, rather than third-line agents (see Figure 8).

Third-line. There is a positive RCT of olanzapine-fluoxetine combination among youth with bipolar depression (level 1)[598]; however, metabolic concerns regarding olanzapine, and limited clinical experience with olanzapine-fluoxetine combination in youth lead to the positioning of this option as third-line. Despite negative findings in paediatric samples, quetiapine (level 2 negative)[599,600] is also recommended as third-line for this population due to the abundance of evidence from adult studies combined with substantial clinical experience. There are also several methodological concerns with the studies done in pediatric samples (see Figure 8).

Despite limited knowledge regarding the precise risks of antidepressant-induced mania in youth with BD, observational pharmaco-epidemiology studies support the conclusion that antidepressants should be used with caution in BDI and BDII, and in combination with mood-stabilizing medication (level 4).[578,601]

Not recommended. A large RCT found that oxcarbazepine was not superior to placebo (level 2 negative)[594] although it was effective in the youngest group of patients but not the older adolescents.

Maintenance treatment

The data in paediatric samples are very limited. These recommendations are therefore informed by clinical experience and studies in adults to a greater extent than the above acute mania recommendations.

First-line. Preferred maintenance treatment options for this population are aripiprazole (level 2),[602,603] lithium (level 2)[604] and divalproex (level 2).[604,605] However, it should be noted that follow-up duration for the aripiprazole study was only 30 weeks, and the sample size in the 18-month maintenance study of lithium vs divalproex was only 30 participants. It is important to note that few patients continued to do well upon the switch to either lithium or divalproex monotherapy and the majority re-responded when the combination was reinstated. Further, other studies have also suggested the efficacy of combination therapy (eg, risperidone plus lithium or divalproex[584] and lithium plus divalproex or carbamazepine[606]) to achieve and maintain remission. Adjunctive lamotrigine may also be considered for those aged ≥ 13 years (level 2).[607]

Second-line. No treatments with level 3 or higher evidence are available to recommend as second-line options for maintenance.

Third-line. Although there has been far less experience with asenapine than with other medications discussed in this section, a recent open-label extension study suggests continual reduction in manic symptoms over 50 weeks (level 4).[608] Further, a recent RCT in adults confirmed its efficacy in preventing relapse of mood episodes.[374] Although there have not been maintenance studies for quetiapine, risperidone, or ziprasidone in this population, clinical experience and open-label studies indicate that continuation and maintenance treatment with these medications is another option, particularly for those patients who have responded well to acute treatment (level 4).[591,609,610] Further, there is evidence that oral quetiapine and long-acting injectable risperidone monotherapy and adjunctive therapy and oral ziprasidone adjunctive therapy are effective in preventing mood episodes in adults with BD.[369,370,383,384,387]

Treatment of comorbid conditions

ADHD. Stimulants may also be used for comorbid ADHD in stable/euthymic youth taking optimal doses of anti-manic medications. Adjunctive mixed amphetamine salts (level 3)[611] and methylphenidate (level 3)[612] have both been shown to be effective in addressing attention symptoms and have been well tolerated overall within the RCTs completed to date, theoretical and epidemiological data regarding risks of induction of mood elevation notwithstanding.[613] Although open trials suggest potential benefits of atomoxetine (level 4),[614,615] the possibility of inducing mania or hypomania remains,[616] suggesting the need for RCTs before clinical recommendations can be made.

Substance use. Comorbid substance use should be treated concurrently to mood symptoms, with inpatient hospital or community residential treatment employed as clinically indicated. A small study suggests that lithium may be effective for reducing substance use in this population (level 3),[617] and FFT should also be considered (Section 2). Positive trials of *N*-acetylcysteine for cannabis use disorders among adolescents,[618] smoking,[619] and bipolar depression among adults [281] suggest that *N*-acetylcysteine may benefit adolescents with comorbid bipolar and SUDs; however, studies examining this hypothesis have not yet been completed (level 4).

7.3 | Management of bipolar disorder in older age

7.3.1 | Presentation and course

Because of the aging population in Canada and many countries around the world, knowledge of pertinent issues related to the management of older adults is becoming increasingly important. Approximately 6% of geriatric psychiatry outpatients and 10% of inpatients have BD,[620] and proportionally this population is one of the highest users of psychiatric and physical health services.[621] Approximately 25% of the patients with BD in the USA in 2005 were over the age of 60 years,[622] and by 2030 >50% of patients with BD are expected to be aged >60 years.[623]

The lifetime prevalence of late-life BD is about 1%-2% with a 1-year prevalence of 0.1%-0.7% in the general population. About 90%-95% of older adults with bipolar disorder have their initial episode prior to age 50 years, although there is a minority who will have a later onset.[624,625] Late onset is often related to neurological or physical comorbidity,[626] and may carry a negative prognosis,[627] although this is not a consistent finding.[628]

While symptoms of mania or hypomania are generally less prominent in older adults, depressive and cognitive symptoms are more often observed, and hyperactivity, aggression, insomnia, impulsivity, and self-neglect may pose a significant risk to the patient and others.[629,630] Psychiatric comorbidity is also generally lower than in younger patients, with anxiety and substance use being the most common.[631] Compared to younger patients, older adults are less likely to utilize inpatient, outpatient, and emergency room services and more likely to use case-management and conservator services.[632]

Cognitive dysfunction is a significant concern for this population, with >30% showing significant deficits across all mood states, including euthymia.[633] This cognitive dysfunction is relatively stable, related to the number of mood episodes earlier in life, and does not appear to exceed normal aging in 2-5-year follow-up.[634-636] Lithium use has been associated with lower rates of cognitive disorders in BD,[637] and higher lithium levels in drinking water may be associated with lower dementia risks,[638,639] although prospective trials are required to definitively assess this. Standardized instruments, such as the Montreal Cognitive Assessment (MoCA), should be used to quantify cognitive dysfunction. Because of the link between cognition and functioning in BD,[634,640] the impact of medications (particularly those with a high anticholinergic burden) on cognition should be considered when making treatment decisions. Furthermore, improvement of modifiable risk factors such as diet, exercise, and mental stimulation should also be promoted in order to further diminish the risk of cognitive decline.

7.3.2 | Medical comorbidity

Older adults with BD have an average of three to four medical comorbidities, with metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine abnormalities being the most common.[631,641] Together, these contribute to a reduction in life expectancy of 10-15 years in BD compared to non-psychiatric populations.[642] Because of these high rates of comorbidities, assessment of an older adult with BD should include a thorough physical and neurological examination, including clinical laboratory tests. Neuroimaging should also be applied as indicated, particularly in the presence of focal neurological signs and symptoms or abrupt late onset, or if the presentation is different from prior episodes. Coordination with other health care providers is also imperative, as this can optimize physical health,[643] as can smoking cessation.

7.3.3 | Pharmacological treatment

The data supporting efficacy of medications in various mood states in this population are limited, with only a single RCT exclusively in geriatric patients completed to date, comparing lithium vs divalproex for the treatment of mania/hypomania.[644] Despite this, open-label trials, naturalistic studies, and post hoc analyses of mixed aged RCTs suggest that medications efficacious in adults overall will also be effective in older adults, although additional considerations regarding medication tolerability and age-related changes in pharmacokinetics and pharmacodynamics must be taken into account. Because of the high number of medical comorbidities as well as physical changes related to the aging process, strict attention must be paid in these patients to potential pharmacokinetic issues, drug-drug interactions, side effects, and the need for ongoing monitoring (see Section 8).

Amongst other effects, lithium has been associated with adverse neurological effects[645] and renal disease.[646] Divalproex has been associated with motor side effects[645] and metabolic effects (weight gain and diabetes mellitus).[647] Carbamazepine induces cytochrome P450 enzymes and can reduce the levels of divalproex and other medications.[648] Regarding antipsychotics, which are now very commonly used for BD in older adults, dose reduction may be beneficial in some aging patients to lower the risk of motor, sedation, metabolic syndrome, and cognitive effects.[649] There is an association between mortality and antipsychotics in patients with dementia[650] but it is unclear how this should be managed for patients with BD. Recently there have also been data linking antipsychotics with acute kidney injury.[651]

In particular, when lithium is used in this population, lithium level and renal monitoring should occur at least every 3-6 months, as well as 5-7 days following a lithium dose adjustment or adjustment of non-steroidal anti-inflammatory drugs (NSAIDs), antiontensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), or thiazide diuretic dosing.[652] Special consideration also needs to be given to dose selection. A post hoc analysis of the STEP-BD study found that while, on average, older patients required a similar number of medications to younger patients to achieve recovery, lower doses were used. In that sample, over twice as many older patients as younger ones recovered using lithium alone (42% vs 21%, respectively).[653] In general, starting at a lower dose (eg, 150 mg nightly for lithium) is recommended, with gradual adjustments to reach the lowest end of the therapeutic range for adults, with subsequent titration based on tolerability and effectiveness; keeping in mind that some older patients will require similar blood levels as the general adult population in order to achieve remission. Further discussion, including clinical guidance and

more detailed treatment recommendations, can be found in the ISBD Task Force report.[654] In light of very limited international guidelines for maintenance treatment of older adults with BD, an ISBD Task Force is currently undertaking a Delphi survey of international experts, and clinicians are advised to consult this as results become available in the future (Shulman K, personal communication).

Pharmacological treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) in older adults as well as safety and tolerability (Section 8). Unfortunately, there is a dearth of literature for efficacy of treatments in older adults. However, clinical experience supports the notion that treatments known to work in general adult populations are also effective in older adults. Tolerability may be different and this is an important consideration in treatment selection in older adults. General principles for management of acute episodes described in Sections 3 and 4 also apply to this population.

Acute mania

Monotherapy with lithium (level 2)[644] or divalproex (level 2)[644] is recommended as a first-line treatment. Quetiapine (level 2)[655] can be considered as second-line. Asenapine (level 4),[656,657] aripiprazole (level 4),[658] risperidone (level 4),[659] or carbamazepine (level 4)[654] may be applied as third-line treatments. For treatment-resistant episodes, clozapine (level 4)[660] and ECT (level 4)[654] should also be considered.

Bipolar depression

There are no RCTs of any agents in older adults with acute bipolar depression. Post hoc analyses of RCTs suggest efficacy of quetiapine (level 2)[661] and lurasidone (level 2)[662] monotherapy and hence these are recommended as first-line options. However, in older adults, given the concerns about side effects of atypical antipsychotics, clinicians may wish to try lithium or lamotrigine first based on their efficacy in adult populations, although the evidence of efficacy is limited in older adults (lithium, level 4; lamotrigine, level 4).[663,664] Divalproex (level 4), aripiprazole (level 4),[658] and carbamazepine (level 4)[665] are third-line options. ECT (level 4)[654] is an important option that should be considered in treatment-resistant cases, for suicidal patients, or for patients with inadequate food or fluid intake.

While the use of antidepressants in BD remains controversial[260,426] and there have been no studies in older age BD; antidepressants are frequently used in this population (>40% of patients).[666] Antidepressants with lower manic switch potential (eg, SSRIs and bupropion)[260] used in combination with mood stabilizers may be beneficial in selected patients who cannot tolerate/do not respond to other agents with a stronger geriatric evidence base. Possible medication interactions with ongoing medications for non-psychiatric conditions must always be considered.

Maintenance

Choice of agents should be based on what has been effective in the acute phase, with recommended options with geriatric efficacy data being lithium (level 2),[667,668] lamotrigine (level 2),[668] and divalproex (level 3).[667]

7.4 | Management of comorbid conditions in bipolar disorder

7.4.1 | Comorbid psychiatric disorders

Epidemiology

Most patients diagnosed with BD will also have at least one comorbid psychiatric diagnosis. The most common comorbid conditions are substance use disorder, anxiety disorder, personality disorder, and impulse control disorder (such as ADHD, ODD, and CD).[45] Comorbidity impacts the course of BDs by increasing the likelihood of treatment resistance and suicide risk, and also by increasing the time spent with impairing symptoms.[34,50,669,670]

When treating comorbid conditions, determining which disorder to address first requires careful consideration. Some comorbid disorders may be managed with the same treatment employed to manage bipolar symptoms (eg, quetiapine for comorbid anxiety and BD), while other comorbid disorders (eg, ADHD) may require distinct treatments. Importantly, some treatments for comorbid disorders may lead to bipolar symptom destabilization; for instance, an antidepressant employed to treat an anxiety disorder may provoke mood elevation.

Safely and effectively managing comorbid conditions often necessitates the implementation of a hierarchical approach, depending on each patient's individual needs and preferences. In general, the disorder or symptom associated with the greatest morbidity and mortality—such as acute mania, psychosis, or suicidal ideation—should be managed first. Substance use disorders may be addressed concurrently or sequentially, depending on severity and contribution to mood instability. Once mood stability is established, the treatment of additional comorbid conditions, such as ADHD or metabolic disorders, should follow based on their impact and the patient's preference.

There is a dearth of research to guide the best management of BD in the context of comorbid conditions. There have been few trials designed with comorbid symptoms as the primary target for mood-stabilizing treatments—evidence is mainly derived from secondary analysis of published data. Thus, the limited research informing the treatment of comorbidities constrains our ability to make definitive recommendations. However, because comorbidity is so common and burdensome for patients, appropriate management is a challenging daily reality in clinical practice. Therefore, CANMAT decided to provide a brief overview of relevant clinical issues and the evidence base for pharmacological treatments for treating comorbid populations. The reader is advised to consult the following references for the role of psychological treatments in managing comorbidity.[671-673]

Substance use disorders

Two recent reviews indicated that the prevalence rate of comorbid SUD in BD is about 33% in general population surveys[674] and approximately 45% in clinical settings.[675] SUD can negatively impact the course of BD, resulting in lower rates of remission,[407] a higher number of hospitalizations,[676,677] and an increased risk of suicide attempts[429] and perhaps suicide deaths.[678]

Substance use should be addressed as early as possible, as it is likely to interfere with treatment for BD. However, the presence of a SUD should not preclude an attempt to treat BD, which might result in an individual being more amenable to treatment. As the directionality of the interaction between SUD and BD is rarely clear in the reality of clinical practice, it is recommended that the two conditions be treated simultaneously.

A more detailed discussion on the impact of and the general principles of the treatment of substance use comorbidity can be found in a CANMAT Task Force publication,[679] and other reviews[673,681] and a meta-analysis[680] published on the topic since 2012. Here we provide a brief update on the pharmacological treatments identified in the CANMAT Task Force publication. It is important to note that the criteria for level of evidence used here are more stringent than those applied to the Task Force report.

The levels of evidence for treatment of comorbid SUD are low. This is because of (i) the paucity of data, (ii) complexity of study designs (given the fact that many patients will be using more than one substance), and, most importantly (iii) inconsistency of the outcome variables used in these studies; hindering direct comparison of results. Nevertheless, some evidence-based recommendations are available for clinicians, starting with general principles of treatment: if at all possible, avoid medications that could increase the risk of destabilizing the BD, and choose treatments that could help both conditions.

Alcohol use disorder

A combination of divalproex and lithium is the only treatment for alcohol use disorder comorbid with BD that meets criteria for level 2 evidence.[682,683] In a small RCT, there was a significant reduction in the number of drinks per drinking day, as well as per heavy drinking day, in the combination group compared to the group with lithium alone when adherence to treatment was added as a covariate. There is only level 3 evidence for lamotrigine,[684] and divalproex monotherapy or add-on.[685-687] While lithium may also show some benefits (level 3),[617] it has to be used with caution in heavy drinkers because of potential electrolyte imbalance; and anticonvulsants warrant liver function tests and lipase levels before initiating treatment. Agents for primary alcohol use disorder may also show benefits in BD, such as disulfiram (level 3),[688-691] naltrexone (level 3)[692-695] and gabapentin (level 4).[696,697] Furthermore, guidelines for pharmacotherapy in alcohol dependence alone can offer some guidance in the absence of comorbidity-specific trials.[698]

Quetiapine is not recommended for the treatment of alcohol use disorder comorbid to BD because of lack of efficacy. Quetiapine add-on therapy was not more effective than placebo add-on in reducing the number of drinks per day or other alcohol-related measures in patients with BDI[699] or BDI and BDII with alcohol dependence (level 1 negative).[700] In another RCT, quetiapine monotherapy or add-on therapy to mood stabilizers was compared with placebo monotherapy or add-on therapy in patients with bipolar depression with comorbid anxiety and substance use disorders.[701] No significant improvement was found in depressive or anxiety symptoms but alcohol or substance use-related outcomes were not reported separately.

No specific recommendations are given regarding acamprosate at this time. In a smaller RCT, acamprosate add-on was ineffective in improving drinking-related outcomes in BDI/BDII patients with alcohol dependence (level 3 negative)[702] but a post hoc analysis showed a small decrease of the Clinical Global Impression scores for substance use severity towards the end of the trial. Further studies are needed.

Cannabis use disorder

About 20% of patients with BD have cannabis use disorder at some point in their life.[675] Cannabis use disorder is associated with younger age, manic/mixed episode polarity, presence of psychotic features, and comorbid nicotine dependence, alcohol use disorder, and other SUDs.[703] Cannabis use is also associated with more time in affective episodes and rapid cycling.[704]

There is limited research into treatment options for this frequent SUD. Lithium and/or divalproex have level 3 evidence.[617,682,685-687] Quetiapine failed to provide any benefit in terms of mood and anxiety symptoms in a small subsample of highly comorbid patients with BD. generalized anxiety disorder (GAD) and cannabis use disorder[701] (level 3 negative). The effect of quetiapine on specific cannabis use-related outcomes was not reported.

Stimulants: cocaine, amphetamine, and methamphetamine use disorders

Citicoline adjunctive therapy had a positive outcome in two RCTs in patients with BD with comorbid cocaine use disorder, although the benefits of citicoline decreased over time in the more recent study (level 2).[705,706]

Lithium or divalproex, either alone or in combination, were proven useful in small studies addressing cocaine use disorder[682,685-687,707,708] (level 4). Quetiapine in monotherapy or in combination with the ongoing treatment shows evidence of efficacy for cocaine, amphetamine and methamphetamine use disorder[709-711] (level 3). Risperidone has been studied alone and as an add-on agent for cocaine and for methamphetamine use disorders with level 3 evidence for efficacy.[711,712]

Bupropion has anecdotal reports favouring efficacy in cocaine use disorders (level 4).[713] Citicoline improved depressive symptoms in patients with methamphetamine use disorder and bipolar depression.[714]

Lamotrigine has been studied in a 10-week RCT of lamotrigine vs placebo added to ongoing medication. While results were negative for the *a priori* outcome variable (positive urine drug screens), they were positive on the secondary outcome of the amount of dollars spent per week on cocaine purchases (level 2 negative).[715]

Opioid use disorder

While methadone has the most evidence of efficacy in comorbid BD and opioid use disorder (level 3),[716,717] because of the lack of research in this area and increasing concern related to risk of overdose, clinicians should consult the Canadian Research Initiative in Substance Misuse (CRISM) national treatment guidelines on primary opioid use disorder when available (anticipated 2018) for further advice on managing opioid use disorders in their patients.

Primary treatments for anxiety disorders: Should they be used to treat co-morbid anxiety in bipolar disorder?

There are no large RCTs that examined the efficacy of SSRIs, SNRIs, pregabalin or lorazepam in treating anxiety symptoms in BD patients with co-morbid GAD. However, several RCTs assessed the efficacy of these agents in patients with primary GAD and have been found to be effective (723). So,should clinicians employ these treatments in treating co-morbid anxiety symptoms in GAD? As with any clinical decision, CANMAT recommends assessing risk-benefit ratio.

Pregabalin is effective and is not associated with risk of mood destabilization and is well tolerated. Hence, pregabalin would be considered an appropriate option although this has not been tested in BD population with co-morbid anxiety. Lorazepam also does not cause mood instability but given the potential dependence with longer-term use, only short-term use of lorazepam may be appropriate. In the case of antidepressants, especially with SNRIs, the risk of manic/hypomanic switch is likely higher. Therefore, if antidepressants are being considered for treating anxiety symptoms, it is recommended to primarily use SSRIs. Further, if SSRIs are used, it is important to ensure adequate mood stabilization with one or more prophylactic antimanic agents (eg. lithium or divalproex or an atypical antipsychotic).

Lorazepam and clonazepam do not provoke mood instability, they are rapidly effective for the acute management of anxiety and they may address early warning signs of mania by inducing sleep. While inappropriate prescribing may result in misuse and dependence and caution must be exercised when prescribing benzodiazepines to elderly patients in particular, the use of benzodiazepines may be appropriate for treating anxiety associated with bipolar disorder. Short-term use is desirable but some patients are unable to tolerate other anxiety treatments and experience significant symptomatic relief and functional improvement due to the judicious use of benzodiazepines.

FIGURE 9 What is the role of primary treatments for anxiety disorders in treating co-morbid anxiety in bipolar disorder? RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Others

Olanzapine add-on therapy was effective in decreasing manic symptoms and measures of substance use such as reduction in cravings in hospitalized inpatients (level 2).[718] Aripiprazole has level 4 evidence to decrease craving of alcohol, but not consumption, and level 4 evidence to decrease cocaine use in polysubstance users.[719]

Anxiety disorders

Patients with BD frequently experience symptoms of anxiety and co-morbid anxiety disorders (GAD, panic disorder, post-traumatic stress disorder and others). Clinical samples indicate that 24%-56% of patients with BD meet criteria for one or more anxiety disorders, with the highest rates in women.[720] Comorbid anxiety symptoms and anxiety disorders are associated with a higher number of mood episodes and depressive symptoms, including suicidality and sleep disturbance, and greater impairment of psychosocial functioning and quality of life.[721] The presence of a comorbid anxiety disorder is also associated with high rates of use of antidepressants,[722] which should be employed with caution due to their potential for mood destabilization (Section 4).

While the CANMAT Task Force report[720] described key studies and treatment recommendations in length, those recommendations have been updated below. However, it remains the case that there are few studies that have focused exclusively on anxiety symptoms or disorders comorbid with BD, whether for treatment efficacy or safety. While there are treatment options, the limitations resulting from a paucity of data prevent the development of clear guidelines or treatment algorithms.

A "step-wise" approach was recommended in the 2012 CANMAT recommendations for managing comorbid anxiety. In general, mood stabilization is the priority before specific anxiety treatments are considered (Figure 9). Despite clinical experience, antidepressants, particularly serotoninergic agents, should be employed with caution due to their potential to provoke mood destabilization. While benzodiazepines are an important clinical tool because they can rapidly alleviate anxiety, clinicians should strive to prescribe them at the lowest possible dose for the shortest period possible, given the concerns about suicide risk, abuse and dependence. CBT continues to be an appropriate first-line treatment for anxiety.

Generalized anxiety disorder and panic disorder

Quetiapine was superior to placebo and divalproex in improving anxiety symptoms in patients with comorbid GAD and/or panic disorder (level 2).[724] Further, secondary analyses from several RCTs indicate that quetiapine monotherapy significantly reduces symptoms of GAD and panic disorder in patients with bipolar depression.[290,313,725] Negative trials include risperidone versus placebo in patients with BD and comorbid GAD and/or panic disorder[726] and ziprasidone versus placebo in a similar trial.[727]

For patients who are euthymic and treated with lithium, the addition of lamotrigine or olanzapine has demonstrated similar anxiolytic effects (level 3).[728] In a secondary post hoc analysis, combinations of olanzapine and fluoxetine (level 3), and to a lesser extent olanzapine monotherapy, were effective in reducing anxiety in patients with bipolar depression.[314]

Gabapentin employed as an adjunctive therapy in open-label studies reduced anxiety symptoms in patients with BD (level 4).[696,729] Given its relatively benign side effect profile and efficacy in other primary anxiety disorders, gabapentin is an appropriate strategy.

Obsessive compulsive disorder

Obsessive compulsive disorder was re-categorized in DSM-5 and is no longer characterized as an anxiety disorder; however, anxiety is a cardinal feature. OCD is a comorbid condition in 10%-20% of patients with BD[730-733] compared with 2%-3% in the general population.[734] However, the prevalence appears to vary widely, depending on the clinical setting and bipolar subtype.[731] Comorbid OCD may be more common in children and adolescents with BD than in adults[731] and has

been reported to co-occur more commonly with BD than other anxiety disorders,[735] although other studies have not found that association.[736]

When diagnosed comorbidly with BD, OCD has been associated with an earlier onset of BD, a higher number of previous mood episodes, rapid cycling, seasonality, substance misuse, and lower overall functioning.[732,737-742] Jeon et al recently conducted a comprehensive review of patients diagnosed with BD and comorbid OCD and found twice the rate of pharmacological switch to mania or hypomania, but suggested this could be due to the more frequent use of antidepressants in that population.[732] Other authors have raised similar concerns.[743]

Symptoms of OCD may precede or follow mood symptoms and the severity of OCD symptoms tends to fluctuate with mood changes.[744] The high rate of co-occurrence and the many shared clinical features of OCD and BD suggest a shared neurobiology. Some researchers have posited that the high rate of co-occurrence might reflect a distinct bipolar phenotype rather than separate disorders.[736,745]

OCD symptoms may remit during effective treatment of BD; mood stabilizers alone or with atypical antipsychotics may be adequate to resolve comorbid symptoms of OCD and antidepressants might not be necessary for the majority of patients.[730,736] If antidepressants are used, clinical experience suggests that SSRIs are preferred, but because of the potential risk of manic switch clinicians need to optimize prophylactic antimanic agents before initiation. The CANMAT Task Force 2012 report included several small case reports indicating the potential benefit of lithium,[743] anticonvulsants,[743,746] olanzapine,[747,748] risperidone,[749,750] quetiapine[751] and aripiprazole [752] for the treatment of comorbid OCD (all level 4 evidence).

Since the 2012 CANMAT publication, there has been very limited new evidence regarding the treatment of comorbid BD and OCD. Two published case reports described successfully employing aripiprazole once monthly[753] and orally[754] for patients with intractable bipolar and OCD symptoms. Another case report described benefits of ECT,[755] and a small trial also found benefits with adjunctive topiramate (level 3).[756]

Personality disorders

A meta-analysis indicates that 42% of patients with BD also have a comorbid personality disorder, and this feature can be both a diagnostic confound and predictor of poorer treatment response. The most prevalent was obsessive compulsive personality disorder (18%), followed by borderline (16%), avoidant (12%) paranoid (11%), and histrionic (10%) personality disorders.[757] Despite the high prevalence of these comorbidities, research assessing the effectiveness of treatments is sparse. The CANMAT Task Force recommendations describe key issues in the management of personality disorders, including the relationship between personality and mood disorders, accurate diagnosis, and the effect on treatment response and clinical course.[758]

The 2012 CANMAT Task Force recommendations for comorbid personality disorder concluded that divalproex (level 3)[466] and lamotrigine (level 4)[759] may provide some symptomatic relief for comorbid borderline personality disorder. Psychoeducation might be of value, as one small RCT that included patients with any comorbid personality disorder (level 3)[760] demonstrated. That study, along with another small trial that combined psychoeducation and skills training for patients with a mood disorder plus a personality disorder and suicidal ideation (level 3),[761] showed a modest long-term benefit. Larger, more specific studies are needed. There are also data to support the utility of DBT for the treatment of BD, which has robust data for efficacy in the treatment of borderline personality disorder.[75,762,763]

Since those CANMAT recommendations were published in 2012, few new studies have significantly contributed to our understanding of the appropriate treatment of these highly comorbid disorders. Alesiani and colleagues assessed the value of the Systems Training for Emotional Predictability and Problem Solving (STEPPS) program for 32 subjects with personality disorder and mood disorder (half MDD and half BD, mostly BDII), and a history of suicide attempts or self-harm and emotional and behavioural dysregulation. Although results are preliminary due to small sample size and high drop-out rate, findings suggest that such group treatment may improve symptoms, as well as reduce suicide attempts and hospitalizations.[761]

ADHD

ADHD and BD co-occur far more commonly than would be expected based on their individual prevalences in the general population. Approximately 10%-20% of patients with BD meet the criteria for adult ADHD and up to 20% of adults with ADHD also meet the criteria for BD.[764] BD and ADHD have a high degree of symptom overlap, making the comorbid diagnosis difficult and requiring careful attention to childhood history and lifetime course of illness. Patients with comorbid ADHD often experience a more treatment-refractory course, more mood episodes, greater functional impairment and a heightened risk of suicide.[765]

The treatment of ADHD presenting comorbidity with BD is discussed in detail in a previous CANMAT Task Force Recommendation paper.[765] Recommendations were to treat bipolar symptoms first with mood stabilizers and/or atypical antipsychotics to stabilize mood before considering treatment for ADHD symptoms. Mixed amphetamine salts (level 3),[611] methylphenidate (level 3),[612] atomoxetine (level 4),[615] bupropion (level 4),[766] or lisdexamfetamine (level 4)[767] add-ons to mood-stabilizing treatments have been reported to be efficacious in improving ADHD symptoms.

In a s Swedish national patient registry study of patients with BD and ADHD, methylphenidate monotherapy significantly increased the risk of mania, while those patients treated concurrently with a mood stabilizer experienced a significantly reduced risk of mania when methylphenidate was employed.[289]

7.4.2 | Comorbid metabolic disorders

Epidemiology

While there is consistent evidence showing the high prevalence of comorbid medical conditions in BD[768-774] and the negative impact these diagnoses have on longevity,[775,776] these conditions frequently go undiagnosed or undertreated. In a large UK cross-sectional analysis of electronic data sets involving 1.7 million patients in primary care, those diagnosed with BD, when compared with healthy controls, had lower rates of diagnoses

(odds ratio [OR] 0.59, 95% confidence interval [CI] 0.54-0.63) and treatment of medical conditions, despite higher rates of one (OR 1.2, 95% CI 1.16-1.39) or multiple illnesses (OR 1.44, 95% CI 1.3-1.64).[769]

Metabolic syndrome in particular is a highly prevalent comorbidity, present in 20-65% of patients with BD.[777] Defined as a cluster of clinical and biochemical features, including abdominal adiposity, hypertension, impaired fasting glucose, diabetes mellitus, and atherogenic dyslipidaemia,[778] metabolic syndrome not only greatly increases an individual's risk for cardiovascular disease, diabetes mellitus, and premature mortality[779] but also worsens bipolar clinical outcomes.[780,781] Increased body mass index (BMI) is an important contributor to metabolic syndrome, although metabolic dysfunction is not always accompanied by overweight/obesity, and so patients with normal BMI should also receive regular monitoring (Section 8).

It has been hypothesized that BD and metabolic syndrome share a set of common risk factors and overlapping pathophysiology.[782-784] While medications used to treat BD, particularly atypical antipsychotics, can also lead to metabolic dysfunction and weight problems (Section 8), insufficient access to primary and preventative health care, low socioeconomic status, habitual inactivity, insulin dysfunction, peripheral inflammation and neuroinflammation, oxidative stress, and childhood adversity are also important contributors.[785]

Principles of management

As noted in previously in these guidelines, older adults commonly have three or more medical comorbidities that contribute to the 10-15 year lower life expectancy compared to non-psychiatric populations.[642] The most common medical comorbidities are metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine disorders.[631,641] This highlights the necessity for vigilance when treating all patients with BD, including regular assessments of their metabolic parameters.

TABLE 23 Baseline laboratory investigations in patients with bipolar disorder

CBC
Fasting glucose
Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
Platelets
Electrolytes and calcium
Liver enzymes
Serum bilirubin
Prothrombin time and partial thromboplastin time
Urinalysis
Urine toxicology for substance use
Serum creatinine
eGFR
24h creatinine clearance (if history of renal disease)
Thyroid-stimulating hormone
Electrocardiogram (>40 years or if indicated)
Pregnancy test (if relevant)
Prolactin

CBC, complete blood count; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; vLDL, very low density lipoprotein (Adapted from Yatham et al. 2006[2]).

Working collaboratively with other members of a patient's health care team is as essential aspect of good clinical care. Comprehensive management of comorbid medical conditions should include a multidisciplinary team-based approach, including primary care, medical specialists, nurses, psychologists, and social workers as appropriate, with patients taking an active role in their care. Treatment strategies should focus both on the psychiatric symptoms and medical issues and risk factors.

A promising strategy for improving the medical care of people with BD is through "primary care-based medical homes" where those with a serious mental illness and at least one other chronic condition receive integrated care. While most studies do not separate BD from other major mental illnesses in analyses, matched samples in the North Carolina Medical Homes programme indicate that patients with BD (n = 13 406) in primary care medical homes had greater use of primary care and specialty mental health care compared with propensity-matched controls, and marginally lower use of emergency services. However, of three diagnostic groups studied (depression, schizophrenia and BD), use of preventative services such as lipid screening and cancer screening was only greater in the subgroup with depression.[786] At the same time, a cross-sectional Canadian study examining patient-centred medical homes in naturalistic practice found that, where rostering was elective, individuals with BD and psychosis were differentially excluded (relative risk [RR] 0.92, 95% CI 0.90-0.93),[787] suggesting that concentrated efforts should be made to ensure appropriate access to these services.

Treatment recommendations

Treatment strategies that target metabolic disorders should include non-pharmacological lifestyle interventions. Replacing "high metabolic risk" psychiatric medications with medications that have a more favourable profile is highly recommended if the therapeutic advantage of the high-risk agent over the alternative is minimal and metabolic/weight issues persist. Bariatric surgery should be considered following unsuccessful attempts at the aforementioned strategies if the individual has a BMI ≥27 with weight-related morbidity or a BMI ≥30 without significant metabolic morbidity. Readers are referred to the CANMAT Task Force report[785] for further detailed discussion on foundational principles for managing metabolic conditions in patients with BD.

While there is no evidence specifically regarding treatment of comorbid dyslipidaemia or hypertension in BD, it is noteworthy that many of the medications used to manage these comorbid medical disorders have epidemiological or even clinical trial evidence that they may benefit mood. Examples include statins, aspirin and angiotensin antagonists.[788-793] The implications are that clinicians should be actively engaged in the management of these disorders, and should select therapies from those agents that may have benefit in mood symptoms. This again is concordant with the notion of shared risk pathways for these non-communicable disorders.

7.4.3 | Other comorbid medical conditions

Two studies from a random sample of 1 million people, taken from a large population-based retrospective cohort in Taiwan, demonstrated a reduced risk of both stroke and cancer associated with lithium treatment for BD. The lithium group was compared with propensity-matched controls.

The first study reported hazard ratio for stroke over 11 years of 0.39 (95% CI 0.22-0.68) for those prescribed lithium, even when adjusting for the risks associated with typical and atypical antipsychotics. The reduced risk was also correlated with a higher dose, longer treatment duration and a higher rate of exposure to lithium.[794] In the second study, in a sample of 4729 patients diagnosed with BD, lithium exposure was associated with a reduced risk of cancer, compared to a group prescribed anticonvulsant medications. (Lithium with or without anticonvulsant HR = 0.735, 95% CI 0.55-0.97). The study also demonstrated a dose-response relationship.[795] In a subsequent large BD cohort study (n = 9651) focusing on genitourinary cancer, however, lithium was not associated with any change in risk.[796]

A recent meta-analysis suggests increased risk of dementia in BD.[797] There is some evidence that lithium in drinking water reduces the risk of dementia in the general population[638] as does the use of lithium in patients with BD.[798]

8 | SAFETY AND MONITORING

8.1 | Medical evaluation and laboratory investigations

A complete medical history including assessment of BMI and baseline laboratory investigations (Table 23) should be performed prior to initiating pharmacological treatment for BD or, in the case of an acute clinical situation, as soon as the patient is cooperative. For more detail, readers are referred to comprehensive guidelines for safety monitoring in BD.[652] In women of childbearing age, pregnancy should be ruled out, and they should be counselled about the possibility of lamotrigine and carbamazepine affecting the efficacy of oral contraceptives before initiating pharmacotherapy.

For those on maintenance therapy with lithium, thyroid and renal function as well as plasma calcium[799] should be assessed at 6 months and at least annually thereafter or as clinically indicated. Menstrual history (to assess for polycystic ovary syndrome), haematology profile, and liver function tests should be obtained at 3-6 month intervals during the first year, and yearly thereafter and as clinically indicated, in patients on maintenance treatment with divalproex. Patients initiated on lamotrigine or carbamazepine should be routinely educated about the risks of skin rashes and the potential for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). They should be advised to contact the treating physician if they observe any type of skin rashes or mucosal ulcers as they require urgent medical evaluation to determine the nature of rashes/ulcers and implementation of most appropriate treatment options which might include discontinuation of these medications and instituting other therapeutic strategies to treat serious rashes and prevent destabilization of BD. Further, prior to commencing carbamazepine, patients with ancestry in genetically at-risk populations such as Han Chinese and other Asian patients should have genotyping performed to ensure that they do not have the human leucocyte antigen (HLA)-B*1502 allele, which confers a high risk for SJS/TEN with carbamazepine.[800] In addition, those on carbamazepine therapy should have serum sodium levels measured at least annually and as clinically indicated given the risk of hyponatraemia with this compound. Patients on atypical antipsychotics should have their weight monitored monthly in the first 3 months and every 3 months thereafter. Blood pressure, fasting glucose and lipid profile should be assessed at 3 and 6 months, and yearly thereafter. Children under 10 years of age, seniors, medically ill patients, and patients on combination treatments should receive more frequent monitoring. Re-emergence of clinical symptoms, as well as signs of haematological, hepatic, cardiovascular, and neurological dysfunction, should also signal the need for additional investigations.

Patients receiving treatment should be regularly monitored for side effects, including weight changes and other adverse events such as extrapyramidal symptoms (EPS).

8.2 | Monitoring medication serum levels

Patients on lithium, divalproex, or carbamazepine need to have their serum medication levels monitored regularly. This is particularly important for those who may be non-adherent to treatment. Measurement of serum levels should be repeated at the trough point, which is approximately 12 h after the last dose. It is recommended that two consecutive serum levels be established in the therapeutic range during the acute phase for lithium and divalproex, and then measurement be repeated every 3-6 months or more frequently if clinically indicated. For carbamazepine, serum level monitoring is mainly done to ensure that the levels are not in the toxic range and to check for treatment adherence as there is no established relationship between efficacy and serum level; thus, monitoring for serum carbamazepine levels may be done at 6-12 monthly intervals and as clinically indicated.

The target serum level for lithium in acute treatment is 0.8-1.2 mEq/L (0.4-0.8 mEq/L in older adults) while in maintenance treatment, serum levels of 0.6-1 mEq/L may be sufficient[801,802]; serum levels should be obtained about 5 days after the most recent dose titration. Clinicians may wish to consult the "lithiumeter" schematic for further guidance.[803] It is important to avoid toxic levels as these are associated with an increased risk of kidney damage in the long term.[804] The target serum level for divalproex is 350-700 mM/L (50-100 ug/mL) in the acute phase and should be obtained 3-5 days after the most recent dose titration. There is some evidence for a linear relationship between serum divalproex level and therapeutic efficacy in acute mania, with higher levels associated with greater efficacy.[805] It is currently unknown what levels of divalproex offer optimum efficacy in maintenance treatment as no study to date has systematically assessed the relationship between serum divalproex level and the maintenance

TABLE 24 Safety/tolerability concerns and risks of treatment-emergent switch with pharmacological agents indicated for use in bipolar disorder

	Safety concerns		Tolerability concerns		Risk of treatment emergent switch	
	Acute	Maintenance	Acute	Maintenance	Mania/hypomania	Depression
Lithium	+	++	+	++	–	–
Anticonvulsants						
Carbamazepine	++	++[a]	+	++	–	–
Divalproex	–	++[a]	+	+	–	–
Gabapentin	–	–	+	+	–	–
Oxcarbazepine	+	+	+	+	–	–
Lamotrigine	++	–	–	–	–	–
Atypical antipsychotics						
Aripiprazole	–	–	+	+	–	–
Asenapine	–	–	+	+	–	–
Cariprazine	–	–	+	–	–	–
Clozapine	++	+++	++	+++	–	–
Lurasidone	–	–	+	+	–	–
Olanzapine	+	+++	++	++	–	–
Paliperidone	–	+	+	++	–	–
Quetiapine	+	++	++	++	–	–
Risperidone	–	+	+	++	–	–
Ziprasidone	++	++	++	+	–	–
Conventional antipsychotics						
Haloperidol	+	+++	++	++	–	++
Loxapine	+	+	+	+	–	nk
Antidepressants (adjunctive[b])						
Agomelatine	+	–	–	–	+	–
Bupropion	+	–	+	–	+	–
Ketamine IV	++	nk	++	nk	nk	nk
MAOIs	++	++	+	++	++	–
SNRIs	–	+	+	–	++	–
SSRIs	–	–	+	+	+	–
TCAs	++	++	++	++	+++	–
Stimulants						
Amphetamines	–	++	+	–	+++	–
Modafinil	–	–	–	–	++	nk
Dopamine agonists						
Pramipexole	–	+	–	–	++	nk

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.
–, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection; nk, not known.
[a]divalproex and carbamazepine should be used cautiously in women of child bearing age (Section 7).
[b]Antidepressant monotherapy is not recommended in bipolar I disorder; for more information on bipolar II disorder, see Section 6.

efficacy. Therefore, clinician are advised to maintain serum divalproex levels within the accepted laboratory range values during maintenance treatment and carefully monitor patients for emerging mood symptoms and tolerability and adjust the dose of divalproex as needed in order to achieve optimum efficacy and tolerability.

Patients who are treated with concurrent carbamazepine or other hepatic enzyme-inducing agents should have serum levels of all psychotropic medications monitored, particularly in cases of inadequate response or non-response, to determine whether efficacy has been compromised because of reduced serum levels.

8.3 | Safety and tolerability of pharmacotherapy

Safety and tolerability issues, in addition to efficacy data, have been considered when determining recommendations for each phase of illness. The most notable concerns are described below and a summary of their potential impact on treatment selection is included in Table 24, as well as in treatment hierarchy tables in Sections 2-4. As medication side effects are an important contributor to medication non-adherence, these potential concerns should be discussed with patients receiving or considering treatment with various agents to help inform decision making.

8.3.1 | Weight gain

As described in Section 6, despite normal weight at illness onset,[806] it is common for patients with BD to become overweight or obese, and several medications used to treat the illness may also exacerbate this effect. The likelihood of medications to cause weight gain should be carefully considered, as this is one of the most frequent treatment-related factors of non-adherence; contributing to upwards of 60% of cases.[807] The medications most commonly associated with weight gain are olanzapine, clozapine, risperidone, quetiapine, gabapentin, divalproex and lithium; with carbamazepine, lamotrigine, and ziprasidone being the safer or options associated with less weight gain.[808] Recent reviews further suggest that asenapine and aripiprazole (longer term use) [809] also may lead to weight gain, but the impact of lurasidone on weight is minimal.[810] All patients should be regularly monitored for weight changes.

8.3.2 | Gastrointestinal symptoms

Both lithium and divalproex are commonly associated with nausea, vomiting, and diarrhoea, with 35%-45% of patient experiencing these side effects.[372,811] For lithium, this is particularly pronounced during treatment initiation, or rapid dose increases.[812] Gradual dose titration, taking the medication at bedtime, taking medications with food, and slow release preparations may reduce nausea and other side effects.[813]

8.3.3 | Renal toxicity

Lithium has a well-recognized potential for renal toxicity, including nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephropathy, and acute tubular necrosis, with NDI reported in 20%-40% of patients.[814-816] Upwards of 70% of patients on chronic lithium treatment will experience polyuria, which can cause impairment in work and daily functioning. This side effect is commonly underreported, unless it is directly inquired about.[817] Long-term administration (ie, 10-20+ years) is further associated with decreased glomerular filtration rate and chronic kidney disease.[818] While long-term lithium administration is probably an important risk factor for developing chronic kidney disease, factors that may increase susceptibility include higher plasma lithium levels, multiple daily lithium doses (vs once daily), concurrent medications (eg NSAIDs, ARBs, ACEIs and diuretics), somatic illnesses (eg, hypertension, diabetes mellitus and coronary artery disease) and older age.[819,820] Instances of lithium toxicity will also greatly increase risk of renal dysfunction.[821] Lithium use is associated with a two-fold higher risk of chronic kidney disease in older adults (>66 years).[822] While the overall risk for progressive renal failure is low, plasma creatinine concentrations and ideally estimated glomerular filtration rate (eGFR) for these patients should be measured at least every 3-6 months.[652] Since 37% of patients aged >70 years have an eGFR <60 mL/min per 1.73 m^2,[823] a strict eGFR cut-off for lithium discontinuation is difficult. The UK National Institute for Healthcare and Excellence (NICE) guidelines for chronic kidney disease (CKD) recommend nephrologist consultation if there is rapidly declining eGFR (>5 mL/min per 1.73 m^2 in 1 year, or >10 mL/min per 1.73 m^2 within 5 years), if the eGFR falls below 45 in two consecutive readings, or if the clinician is concerned.[646,824]

Because of its narrow therapeutic window, acute lithium intoxication is also a complication, which, though reversible, can lead to reductions in glomerular filtration rate.[825,826] Drugs that alter renal function and general medical conditions characterized by decreased circulating volume all contribute to increased risk.[827]

8.3.4 | Haematological effects

Carbamazepine may be a risk factor for leucopenia,[828-830] although this finding is not robust.[831] This side effect is generally reversible with dose reduction or discontinuation. There is also some concern about rapidly developing bone marrow suppression resulting from hypersensitivity, particularly in older patients.[831,832]

Clozapine carries the greatest risk for drug-induced changes in white blood cell counts, with approximately 0.18% of patients experiencing changes rated as probably or definitely drug induced.[828] All patients started on clozapine should have a baseline haematological profile established and be enrolled in the clozapine monitoring programme which requires regular monitoring of haematological parameters: weekly at first and then every 2-4 weeks later in the course of treatment.[833]

8.3.5 | Cardiovascular effects

Lithium can increase the risk of abnormal QT prolongation or T-wave abnormalities,[834] an impact more pronounced with age, as almost 60% of older patients on lithium maintenance therapy have ECG abnormalities.[835] Several antipsychotics, including risperidone, olanzapine, ziprasidone and asenapine, are also associated with arrhythmias, QTc prolongation, and other cardiovascular adverse events. Clozapine may increase the risk of several rare but serious events such as dilated cardiomyopathy, myocarditis, and pericarditis. Of the antipsychotics, lurasidone and aripiprazole are considered safe from a cardiac perspective, although aripiprazole may increase the risk for hypotension.[810]

8.3.6 | Endocrine effects

There is also a strong link between lithium maintenance treatment and hypothyroidism, which is also associated with increased risk of affective episodes, rapid cycling, and more severe depression.[836,837] Routine screening of thyroid function is therefore recommended for all patients on lithium treatment. Since lithium can also cause hyperparathyroidism, routine monitoring for serum calcium is recommended, and, if elevated, further investigations should be performed to evaluate for hyperparathyroidisim.[838] Hypothyroidism is ordinarily not an indication for lithium cessation in a patient with a good response; rather, thyroid supplementation is recommended.

New onset oligomenorrhoea or hyperandronism is more common in divalproex users.[839] While there are reports of an increased incidence of polycystic ovary syndrome (PCOS) in divalproex treatment, a recent meta-analysis did not support this.[840] In those who develop PCOS on divalproex, there is evidence from a small sample that discontinuing divalproex results in remission of some of the aspects of PCOS.[841]

Hyperprolactinaemia is common with some antipsychotics, and can have short-term and long-term adverse effects. Risperidone, amisulpride and paliperidone are more likely than other compounds to cause it.[842] Hyperprolactinaemia can induce amenorrhoea, sexual dysfunction, and galactorrhoea, amongst other effects. In the long term, it can cause gynaecomastia and osteoporosis.[843] When such effects are seen, it may advisable to reduce the dose or switch to a different medication.[844]

8.3.7 | Cognition

While many patients experience cognitive impairment, these deficits may be attributable to the disease itself, with more pronounced effects in those with more severe or chronic illness.[845] While a small study has led to suggestions that medicated patients who are euthymic do perform similarly to those not receiving treatment,[846] other naturalistic trials point towards the potential negative impact of several medications, with the effects of antipsychotics being the most significant.[845] Lithium can also lead to impairment in processing speed and memory, which patients may find distressing,[847] although recent randomized controlled data suggest lithium is superior to quetiapine in this regard.[329] Indeed, the effects of lithium on neurocognition are complex and further research is needed to fully elucidate its neurocognitive impact.[848] Anticonvulsants, except for lamotrigine, are also linked to subjective cognitive impairment.[847] Given the importance of cognition on a patient's function and quality of life, further studies are needed in this area.

8.3.8 | Sedation

Sedation is a concern for many, and is reported by over half of patients as a reason for treatment non-adherence.[807] Divalproex and atypical antipsychotics are most likely to lead to these effects, with 30%-50% of patients on atypical antipsychotics experiencing sedation, compared to 8%-13% with placebo[164,214,849-851] and 21%-29% of patients on divalproex.[852,853] This is not a concern with all antipsychotics, however; quetiapine, clozapine, and olanzapine will generally have higher rates of sedation compared to ziprasidone, risperidone, and aripiprazole.[810] Lamotrigine and lithium have both been found to be less likely to cause sedation than divalproex.[854,855]

8.3.9 | Neurological effects, including EPS

Tremor can be a significant cause of frustration for many patients, and is experienced by up to 10% of those treated with lithium or divalproex.[668,856,857] New onset neurological symptoms in patients on divalproex should raise suspicion of hyperammonaemic encephalopathy, which, while rare, can be potentially fatal, and hence early detection and discontinuation of divalproex is critical to prevent morbidity and mortality[858] Sustained release formulations and dose reductions may limit symptoms.[802,859,860] While conventional antipsychotics such as haloperidol are often associated with EPS (including pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia),[861] this risk is either absent or low with atypical antipsychotic agents.[862,863] Among the atypical agents, risperidone, aripiprazole, cariprazine, ziprasidone and lurasidone are more likely to cause EPS, particularly at higher doses.[810] In older patients, impaired swallowing function and dysphagia have also been linked to atypical agents, particularly at higher doses.[864,865]

Although rare, neuroleptic malignant syndrome (NMS) is a potentially life-threatening adverse event associated with antipsychotic agents. The risk with atypical agents was considered negligible initially; however, while the risk is very low, several atypical agents have nevertheless been associated with NMS.[866] While generally unpredictable, the risk is greatest during the initial phase of treatment or change of dosage, with intravenous or intramuscular administration, with high dosages or polypharmacy, when the patient is physically restrained or dehydrated, in high ambient temperatures, in older patients and in patients with medical or psychiatric comorbidities. Patients with a previous history of NMS and/or a personal or family history of catatonia are also at higher risk.[867] Antipsychotics may also impact thermoregulation, with case studies indicating the potential for both heat-related illnesses[868] and hypothermia[869]; thus, patients should be made aware and monitored for these risks during periods of extreme temperatures.

8.3.10 | Dermatological reactions

Approximately 10% of patients being treated with lamotrigine will experience a non-serious rash, with 0.3%-1% developing a serious rash such as toxic epidermal necrolysis and SJS,[870] although for those initiated on a dose of 25 mg with a gradual titration increasing the dose by 25 mg biweekly, the risk of developing serious rash may be as low as 0.02% or 1 in 5000.[871] In some cases, an even lower rate of titration may be used (ie 12.5 mg/day and then gradually increase as per instructions. Carbamazepine is also associated with increased risk of rash and SJS, especially in the first 8 weeks of therapy,[872] although the baseline risk is extremely low. Similarly, while these can also occur with divalproex, the risk is extremely low. Nevertheless, it is important that patients be

informed of these risks and told to report any rash immediately, and these treatments should be discontinued if a serious rash is suspected.

Lithium is also linked with a variety of potentially distressing skin conditions, including acne, psoriasis, eczema, hair loss, hidradenitis suppurativa, nail dystrophy and mucosal lesions, with overall estimates ranging from 3% to 45% depending on the criteria applied. Most cases can be managed without treatment discontinuation.[873]

8.3.11 | Metabolic syndrome, hyperglycaemia, type 2 diabetes and dyslipidaemia

As described in Section 6, patients with BD are already at elevated risk for these physical illnesses and this risk is further exacerbated by some atypical antipsychotic agents and mood stabilizers. Clozapine and olanzapine are associated with the greatest level of risk, followed by quetiapine (particularly in higher doses) and risperidone, with a more minimal impact of aripiprazole, ziprasidone, asenapine, and lurasidone.[810] Lithium and divalproex are also associated with weight gain.[791] All patients on atypical antipsychotics should be monitored for changes in blood glucose and lipid profiles as indicated previously in this section, and if disturbances are detected, the atypical antipsychotic should be discontinued if possible and appropriate treatment initiated if necessary.

8.3.12 | Fracture risk and osteoporosis

Some anticonvulsants, antidepressants, and antipsychotics may decrease bone mineral density and increase the risk of fracture in high-risk patients.[874,875] This risk is increased by the presence of mood disorders, as well as known risks for mood disorders such as physical inactivity, smoking and poor diet quality.[876] Thus, screening for this population may be indicated.[877]

9 | CONCLUDING REMARKS

The diagnosis and management of BD is complex, and effective, evidence-based care requires knowledge of current research as well as lessons gained from years of clinical experience. Members of the CANMAT guidelines committee hope this document does an effective job at providing an easy to understand narrative of both, thus aiding both specialists and primary care providers in delivering evidence-based care to their patients. As with previous editions of these guidelines, CANMAT will strive to provide regular updates capturing emerging trends and evaluating new evidence; and readers are encouraged to consult those as they become available to stay up to date in the field.

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