The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence

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Bipolar disorder is a complex and heterogeneous psychiatric condition that affects more than 2% of the population. The assessment and treatment of bipolar disorder can be a challenge for clinicians, given its clinical complexity and the rapidly changing treatment landscape with the growing range of treatment options that are becoming available for various phases of the illness. To help clinicians navigate the complexity involved in the assessment and management of bipolar disorder, the guidelines of the 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) synthesized the evidence on the efficacy, safety, and tolerability of treatments for bipolar disorder and translated it into first-, second-, and third-line treatment recommendations. The main objective of this contribution is to provide clinicians with a summary of the 2018 CANMAT/ISBD guideline recommendations with the addition of any new evidence for the treatment of bipolar disorder across the lifespan.

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The Canadian Network for Mood and Anxiety Treatments (CANMAT) has been publishing treatment guidelines for bipolar disorder since 2005, with timely updates as new evidence becomes available. The last two updates (2009 and 2013) as well as the latest full edition (2018) of the CANMAT guidelines were published in collaboration with the International Society for Bipolar Disorders (ISBD). The main objective of these publications has been to provide comprehensive yet practical recommendations for clinicians with the aim of optimizing care for patients with bipolar disorder. The 2018 CANMAT/ISBD guidelines (1) provided comprehensive review of research evidence as the basis for international consensus on evidence-based assessment and treatment of bipolar disorder. The final ranking of treatment recommendations into first-, second-, and third-line took into account levels of evidence for efficacy and clinical experience, as well as considerations for safety, tolerability, and risk of treatment-emergent affective switch. Definitions for level of evidence ratings as well as line of treatment ratings used in those guidelines are provided in Table 1. In addition, the 2018 CANMAT/ISBD guidelines offered hierarchical rankings for first- and second-line recommendations for acute mania and depression as well as maintenance treatment for bipolar I disorder. The hierarchical approach proposed by the 2018 CANMAT/ISBD guidelines took into account not only the efficacy of each agent for the phase being treated but also the efficacy for other phases of the illness along with both the short- and longer-term tolerability and safety of the agent. Given that bipolar disorder is a lifetime condition, this approach ranks treatments that have demonstrated efficacy across the spectrum of the illness higher and recommends using them before using those that have demonstrated efficacy for only selective phases of the disorder. If two agents have shown similar efficacy across the phases, then tolerability and safety considerations determine the hierarchical ranking.

The current contribution provides a summary of the 2018 CANMAT/ISBD guideline recommendations for the treatment of bipolar disorder across the lifespan, with the aim of helping clinicians incorporate these recommendations into their clinical practice. The evidence base and rationale for these recommendations can be found in the original publication and are not included in this summary. Additionally, as it has now been 5 years since the publication of the 2018 CANMAT/ISBD guideline recommendations, we incorporated findings from relevant randomized controlled trials (RCTs) and meta-analyses that have been published in the past 5 years into the recommendations.

EPIDEMIOLOGY

Bipolar disorder is a chronic and disabling psychiatric condition that typically manifests in late adolescence and young adulthood, with an average age at onset of 25 years. According to the American Psychiatric Association's fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) (2), bipolar disorder encompasses bipolar I disorder, which is defined by the presence of at least one threshold manic episode, and bipolar II disorder, which is characterized by hypomanic episodes and threshold

TABLE 1. Definitions of level of evidence and line of treatment ratings according to the 2018 CANMAT/ISBD guidelines

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
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 and/or 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 specifically notes when lack of clinical support for safety and/or tolerability or risk of treatment-emergent switch has affected recommendations.
CANMAT=Canadian Network for Mood and Anxiety Treatments; ISBD=International Society for Bipolar Disorders.

depressive episodes. Subthreshold bipolar-related disorders include cyclothymic disorder as well as "other specified bipolar and related disorder" and "unspecified bipolar and related disorder" (2). The World Mental Health Survey Initiative reported total lifetime (and 12-month) prevalence estimates of 0.6% (0.4%) for bipolar I disorder, 0.4% (0.3%) for bipolar II disorder, and 1.4% (0.8%) for subthreshold bipolar disorder (3).

DIAGNOSTIC ASSESSMENT

Because of several factors such as frequency of depressive episode onset, variable help-seeking behavior during hypomanic episodes, symptom overlap with other conditions, and high rates of comorbidity, the accurate and timely identification of bipolar disorder often remains elusive. Many individuals with bipolar disorder do not receive the accurate diagnosis for several years after the onset of symptoms (4). This delay has major consequences, including inadequate or inappropriate treatment and poor outcomes. The most common misdiagnosis is major depressive disorder (5). In general, patients are more likely to seek help for the treatment of depressive symptoms and may not recall periods of hypo(mania) or interpret them as being pathological. There are certain clinical features of depressive episodes that raise suspicion of a bipolar illness and, therefore, should prompt more careful investigation. Those features include earlier onset of first depressive episode (<25 years); highly recurrent depressive episodes (≥5 episodes); a family history of bipolar disorder; 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. Other common misdiagnoses include anxiety disorders, primary psychotic disorders such as schizophrenia, personality disorders, and substance-related mood disorders (5).

In addition to underdiagnosis, over-diagnosis of bipolar disorder can also be a concern in some circumstances (6), partly because of symptoms overlapping with those of other conditions, such as borderline personality disorder, substance-related disorders, and attention-deficit hyperactivity disorder (ADHD). Screening tools such as the Mood Disorders Questionnaire have poor sensitivity and specificity (7) but, nevertheless, can help flag those individuals for whom a more detailed assessment is needed. It is important for clinicians to complete a careful psychiatric history and, when possible, try to incorporate input from family members and significant others in the diagnostic evaluation as well as during the treatment process. At times, prospective monitoring of mood symptoms, ideally through daily mood charting, would be required to confirm the diagnosis.

Many individuals with bipolar disorder have one or more comorbid psychiatric conditions. The presence of these comorbid conditions adds to the complexity of bipolar disorder and makes the diagnosis even more difficult to establish. Substance use disorders are one of the most common comorbid conditions in patients with bipolar disorder, with an estimated prevalence rate of about 33% in the general population (8) and 45% in clinical settings (9). Comorbid substance use disorder is associated with lower rates of remission (10), a higher number of hospitalizations (11, 12), and an increased risk of suicide attempts (13). Anxiety disorders also show prevalent comorbidity with bipolar disorder, as between 24% and 56% of individuals with bipolar disorder have comorbid anxiety disorders (14). The presence of anxiety disorders is associated with higher number of mood episodes and depressive symptoms

BOX 1. Pharmacological treatment of acute mania[a]

First-Line (Hierarchical Ranking)
Monotherapy
- Lithium
- Quetiapine
- Divalproex
- Asenapine
- Aripiprazole
- Paliperidone (>6 mg)
- Risperidone
- Cariprazine

Combination Therapy
- Quetiapine + Li/DVP
- Aripiprazole + Li/DVP
- Risperidone + Li/DVP
- Asenapine + Li/DVP

Second-Line (Hierarchical Ranking)
- Olanzapine
- Carbamazepine
- Olanzapine + Li/DVP
- Lithium + DVP
- Ziprasidone
- Haloperidol
- ECT

Third-Line
- Carbamazepine/oxcarbazepine + Li/DVP
- Chlorpromazine
- Clozapine
- Haloperidol + Li/DVP
- rTMS
- Tamoxifen
- Tamoxifen + Li/DVP

Not Recommended
- Allopurinol
- Eslicarbazepine/licarbazepine
- Gabapentin
- Lamotrigine
- Omega-3 fatty acids
- Topiramate
- Valnoctamide
- Zonisamide

[a] The first- and second-line agents are listed hierarchically. Third-line agents are in alphabetical order. DVP=divalproex; ECT=electroconvulsive therapy; Li=lithium; rTMS=repetitive transmagnetic stimulation.

(including suicidality) and greater impairment of psychosocial functioning and quality of life (15). Other conditions that are commonly comorbid with bipolar disorder include personality disorder (42%) (16) and ADHD (10%–20%) (17).

SUICIDE RISK

Suicide is one of the leading causes of death in individuals with bipolar disorder; therefore, it is important for clinicians to monitor frequently for suicidal ideation and risk. In the World Health Organization's World Mental Health Survey Initiative, about 43% of patients with bipolar disorder reported suicidal ideation, 21% reported having a plan, and 16% reported an attempt within the past year (3). The periods during and following hospital admission are particularly high risk. Female sex, younger age at illness onset, depressive polarity of first or more recent episode, first-degree family history of suicide, and previous suicide attempts, as well as comorbid anxiety disorder, substance use disorder, and borderline personality disorder, are associated with suicide attempts (18). Only male sex and first-degree family history of suicide have been significantly associated with suicide deaths (18, 19). A comprehensive assessment for suicide risk focused on identifying and reducing modifiable risk factors should occur during all clinical encounters. Treatment with lithium and, to a lesser extent, anticonvulsants may contribute to preventing suicide attempts and deaths (20).

PSYCHOSOCIAL INTERVENTIONS

Although pharmacotherapy is the foundation of, and is essential for, the successful treatment of bipolar disorder, adjunctive psychosocial interventions may be useful for acute depressive episodes and in maintenance. Positive evidence exists for psychoeducation (first-line), cognitive-behavioral therapy (CBT; second-line), family-focused therapy (FFT; second-line), interpersonal and social rhythm therapy (third-line), and peer interventions (third-line) in the maintenance phase of bipolar disorder. CBT and FFT are also recommended as second-line adjunctive treatments for acute depression.

PHARMACOLOGICAL TREATMENT OF MANIC EPISODES

Recommendations for pharmacological treatment of acute mania are outlined in Box 1.

Step 1: Review General Principles and Assess Medication Status

A thorough assessment including risk of violence, self-harm, insight, and the ability to adhere to treatment, and comorbidity should be conducted to establish the most appropriate treatment setting. Physical examination and laboratory investigations can be deferred for uncooperative patients. Antidepressants in a patient presenting with acute mania should be discontinued. Patients should also be supported to discontinue substances such as stimulants (including caffeine) and alcohol. Past response to and tolerability of medications used in current and prior episodes should be assessed and used to direct subsequent therapeutic choices.

Step 2: Initiate or Optimize Therapy and Check Adherence

Both monotherapy and the combination of a mood stabilizer and an atypical antipsychotic are appropriate first-line

treatments for acute mania. Specific medications include lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine as first-line monotherapy options and a combination of quetiapine, aripiprazole, risperidone, or asenapine with lithium or divalproex as first-line combination therapy options.

As previously stated in the introduction, the first- and second-line recommendations are listed hierarchically on the basis of the efficacy of each agent in treating acute mania as well as treating bipolar depression, relapse prevention, safety and tolerability, and risk of treatment-emergent affective switch. The 2018 CANMAT/ISBD guideline recommends that treatments listed higher up in Box 1 need to be considered first, unless other factors such as history of previous nonresponse or patient's preferences dictate otherwise.

If symptoms are not controlled with first-line agents, dosing should be optimized. In case of no improvement in symptoms within the first 2 weeks of receiving therapeutic doses, factors such as possible nonadherence and ongoing substance use should be considered before adding or switching medications.

Step 3: Add on or Switch Therapy (Alternate First-Line Agents)

If treatment with one or a combination of first-line agents at optimal doses is inadequate or intolerable, the next step is to switch to or add on an alternate first-line treatment.

Step 4: Add on or Switch Therapy (Second-Line Agents)

When all first-line options have failed, second-line choices—including monotherapy with olanzapine, carbamazepine, ziprasidone, and haloperidol; combination therapy with olanzapine plus lithium or divalproex or with lithium plus divalproex; or electroconvulsive therapy (ECT)—should be considered.

Step 5: Add on or Switch Therapy (Third-Line Agents)

Third-line options for treatment of acute mania are outlined in Box 1. These agents should only be used if there has been no response to adequate trials with all first- and second-line agents alone and in combination.

Update on Studies Showing Efficacy of Drugs in Acute Mania

A recent meta-analysis (21) showed that augmentation therapy with antipsychotics and mood stabilizers is more effective than monotherapy (Level 1) in treating manic symptoms without any significant difference in tolerability at weeks 3 and 6.

PHARMACOLOGICAL TREATMENT OF ACUTE BIPOLAR DEPRESSION

Recommendations for pharmacological treatment of acute bipolar depression are outlined in Box 2.

BOX 2. Pharmacological treatment of acute bipolar I depression[a]

First-Line (Hierarchical Ranking)
- Quetiapine
- Lurasidone + Li/DVP
- Lithium
- Lamotrigine
- Cariprazine (new)
- Lurasidone (adj)

Second-Line (Hierarchical Ranking)
- Divalproex
- SSRIs/bupropion (adj)
- ECT
- Olanzapine-fluoxetine
- Lumateperone (new)

Third-Line
- Aripiprazole (adj)
- Armodafinil (adj)
- Asenapine (adj)
- Carbamazepine
- Eicosapentaenoic acid (adj)
- Ketamine (IV) (adj)
- Levothyroxine (adj)
- Light therapy with or without total sleep deprivation (adj)
- Modafinil (adj)
- N-acetylcysteine (adj)
- Olanzapine
- Pramipexole (adj)
- rTMS (adj)
- SNRI/MAOI (adj)

Not Recommended
- Antidepressant monotherapy
- Aripiprazole
- Lamotrigine + folic acid
- Mifepristone (adj)

[a] The first- and second-line agents are listed hierarchically. Third-line agents are listed in alphabetical order. Adj=adjunctive; DVP=divalproex; ECT=electroconvulsive therapy; IV=intravenous; Li=lithium; MAOI=monoamine oxidase inhibitor; rTMS=repetitive transmagnetic stimulation; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonergic reuptake inhibitor.

Step 1: Review General Principles and Assess Medication Status

A thorough assessment of the nature and severity of depression and associated symptoms, risk of self-harm, ability to adhere to a treatment plan, availability of a psychosocial support network, and functional impairment should be conducted to establish the most appropriate treatment setting. Laboratory investigations should also be completed. Patients should be supported to discontinue substance use. Past response to and tolerability of medications used in current and prior episodes should be assessed and used to direct subsequent therapeutic choices.

Step 2: Initiate or Optimize Therapy and Check Adherence

Patients presenting with acute bipolar depression should be initiated on one of the first-line treatments. Quetiapine, lithium, lamotrigine, and lurasidone are recommended as first-line monotherapy options; lurasidone and lamotrigine are also recommended as first-line adjunctive treatments.

The first- and second-line recommendations are listed hierarchically. The 2018 CANMAT/ISBD guideline recommends that treatments listed higher up in Box 2 need to be considered first, unless other factors such as history of previous nonresponse or patient's preferences dictate otherwise.

Step 3: Add on or Switch Therapy (Alternate First-Line Agents)

In case of a lack of response to the first trial, the next step is to switch to or add on an alternate first-line treatment. In principle, a switch is preferred over an add-on to limit the degree of polypharmacy unless there was a partial response.

Step 4: Add on or Switch Therapy (Second-Line Agents)

In case of inadequate response to first-line options, monotherapy with divalproex or adjunctive antidepressants (selective serotonin reuptake inhibitors [SSRIs] or bupropion) can be considered as a second-line option. The ISBD Antidepressant Task Force (22) recommends that antidepressants should be avoided or used cautiously in patients with a history of antidepressant-induced mania, current or predominant mixed features, or recent rapid cycling.

It is important to inform patients (and families, if appropriate) of the risk of treatment-emergent affective switch and advise that antidepressants should be discontinued should early warning signs of mania emerge. Antidepressants should *not* be used as monotherapy for the treatment of bipolar I depression.

Finally, ECT is also a second-line treatment, particularly for patients with treatment-refractory bipolar depression and those with severe depression with imminent risk of suicide, catatonia, or psychotic depression or when a rapid response is important for medical stabilization.

Step 5: Add on or Switch Therapy (Third-Line Agents)

Third-line options for treatment of acute bipolar depression are outlined in Box 2. These agents should be considered only after multiple first- and second-line options have been trialed first.

Update on Studies Showing Efficacy of Drugs in Bipolar I Depression

Three RCTs (23–25) have shown the superior efficacy of cariprazine compared with placebo in the treatment of bipolar I depression. The most common treatment-emergent side effects were akathisia, nausea, fatigue, and sedation. Cariprazine was recommended as a second-line treatment option in the 2018 CANMAT/ISBD guidelines because of less clinical experience; it has been upgraded to a first-line option, given the data and clinical experience since then.

Lumateperone is a novel antipsychotic acting on various serotonin and dopamine receptors. It is a potent 5-HT_{2a} antagonist, dopamine D_2 receptor presynaptic partial agonist, and postsynaptic antagonist; a D_1 receptor–dependent indirect modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (or, AMPA) and *N*-methyl-D-aspartate (or, NMDA) currents; and a serotonin reuptake inhibitor (26). A recently published RCT (Level 2) has shown greater efficacy of lumateperone (at 42 mg) in bipolar I and bipolar II depression compared with placebo (27). In this study (27), lumateperone monotherapy (N=188) was associated with significant improvement in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) compared with placebo (N=189). In the second study (28), patients with bipolar depression who had inadequate response to lithium or valproate showed significantly greater improvements in MADRS score with adjunctive lumateperone (N=177) (Level 2) compared with adjunctive placebo (N=176). The common adverse events of lumateperone include nausea and somnolence, with an advantage of low incidence of extrapyramidal symptoms and an increase in prolactin (27, 28).

PHARMACOLOGICAL TREATMENT FOR MAINTENANCE THERAPY

Almost all individuals with bipolar disorder require maintenance treatment to prevent relapse and restore functioning and quality of life. Ongoing psychoeducation and flexible, collaborative engagement with patients are recommended to optimize the acceptability of maintenance pharmacological treatment.

Step 1: Review General Principles and Assess Medication Status

In general, it is recommended that medications that have been effective in the acute phase be continued during the maintenance phase (except for long-term use of antidepressants, which is generally not recommended in treating bipolar disorder). For patients who are not receiving or responding to pharmacological treatment, a detailed history of clinical course, response to previous trials, and family history should be collected. Other factors to consider would include comorbidity, the predominant mood polarity, and the polarity of the most recent mood episode.

Step 2: Initiate or Optimize Therapy and Check Adherence

As with treatment for acute mania and depression, the 2018 CANMAT/ISBD guideline recommends that treatment

choices for maintenance treatment of bipolar disorder should follow the hierarchy listed in Box 3, unless patient preference or clinical factors such as previous response, tolerability, or predominant polarity warrant other options. In addition, if a patient has been treated for an acute mood episode and responded to a first-line maintenance treatment, the recommendation is to continue that treatment for maintenance even if lower down in the hierarchy. At times, it may be necessary to lower the dose to some degree during maintenance treatment if there are tolerability concerns, as treatment adherence may be a challenge if doses are not adjusted.

There is evidence that the risk of recurrence is lowered when an antipsychotic is combined with lithium or divalproex. When a combination of an atypical antipsychotic with lithium or divalproex was used to treat acute mania, continuing the atypical antipsychotic for the first 6 months after response reduced the risk of relapse (29), but the benefits beyond 6 months remain uncertain.

Lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole (oral or once-monthly injection) monotherapies are recommended as first-line maintenance treatments. Combination therapies recommended as first-line include quetiapine or aripiprazole combined with lithium or divalproex.

For patients who experience a relapse or remain symptomatic while on a first-line maintenance treatment, the next step is to optimize the dose and address potential issues with adherence before moving to step 3.

Step 3: Add on or Switch Therapy (Alternate First-Line Agents)

If treatment with the first-line agent (or combination of agents) at optimal doses proves to be inadequate or intolerable, the next step is to switch to or add on an alternate first-line agent.

Step 4: Add on or Switch Therapy (Second-Line Agents)

After unsuccessful trials of multiple first-line options, second-line choices—including olanzapine, long-acting injectable risperidone monotherapy or adjunctive therapy, carbamazepine, paliperidone, adjunctive ziprasidone, and adjunctive lurasidone—should be considered.

Step 5: Add on or Switch Therapy (Third-Line Agents)

Third-line options for maintenance treatment of bipolar disorder are outlined in Box 3.

Update on Studies Showing Efficacy of Drugs in Maintenance of Bipolar I Disorder

When combination therapy of an atypical antipsychotic with lithium or divalproex was used to treat acute mania, CANMAT/ISBD 2018 guidelines recommended continuing the atypical antipsychotic for the first 6 months and then re-evaluating, as the benefits of maintenance combination therapy beyond 6 months remains uncertain (29). However, a recently published meta-analysis (30) showed that combination of atypical antipsychotics and mood stabilizers is associated with lower rates for recurrence of any mood episode and all-cause discontinuation at 1, 2, 3, 9, and 12 months when compared with placebo and mood stabilizers (Level 1).

BOX 3. Pharmacological treatment for maintenance therapy in bipolar I disorder[a]

First-Line (Hierarchical Ranking)
- Lithium
- Quetiapine
- Divalproex
- Lamotrigine
- Asenapine
- Quetiapine + Li/DVP
- Aripiprazole + Li/DVP
- Aripiprazole
- Aripiprazole OM

Second-Line (Hierarchical Ranking)
- Olanzapine
- Risperidone LAI
- Risperidone LAI (adj)
- Carbamazepine
- Paliperidone (>6 mg)
- Lurasidone + Li/DVP
- Ziprasidone + Li/DVP

Third-Line
- Aripiprazole + lamotrigine
- Clozapine (adj)
- Gabapentin (adj)
- Olanzapine+fluoxetine

Not Recommended
- Perphenazine
- Tricyclic antidepressants

[a] The first- and second-line agents are listed hierarchically. Third-line agents are in alphabetical order. Adj=adjunctive; DVP=divalproex; LAI=long-acting injection; Li=lithium; OM=once monthly.

PHARMACOLOGICAL TREATMENT OF BIPOLAR II DISORDER

Bipolar II disorder is distinct from bipolar I disorder. The diagnosis of bipolar II disorder requires one or more episodes of hypomania, one or more episodes of depression, and an absence of manic episodes. The treatment of bipolar II disorder has been understudied, which makes it challenging to provide evidence-based recommendations. Therefore, compared with bipolar I disorder, there are fewer first-line treatment recommendations for bipolar II disorder.

Acute Management of Hypomania

Although, for some patients, hypomania may be associated with only minimal functional impairment or even brief periods of above-normal functioning, others may

BOX 4. Pharmacological treatment of bipolar II depression and maintenance

First-Line
Acute Depression
Quetiapine

Maintenance Therapy
Quetiapine
Lithium
Lamotrigine

Second-Line
Acute Depression
Lithium
Lamotrigine
Bupropion (adj)
ECT
Sertaline[a]
Venlafaxine[a]
Lumateperone (new)

Maintenance Therapy
Venlafaxine

Third-Line
Acute Depression
Agomelatine (adj)
Bupropion (adj)
Divalproex
EPA (adj)
Ketamine (IV or sublingual) (adj)
N-acetylcysteine (adj)
Pramipexole (adj)
T3 and T4 thyroid hormones (adj)
Tranylcypromine
Ziprasidone[b]

Maintenance Therapy
Carbamazepine
Divalproex
Escitalopram
Fluoxetine
Other antidepressants
Risperidone[c]

[a] For patients with pure depression (nonmixed).
[b] For patients with depression and mixed hypomania.
[c] Primarily for prevention of hypomania.
Adj=adjunctive; ECT=electroconvulsive therapy; EPA=eicosapentaenoic acid.

experience rather prolonged, relatively severe, or irritable or mixed hypomania that can be impairing. Most standard antimanic agents have not been studied in hypomania. However, clinical experience suggests that all antimanic medications can also be effective for the treatment of hypomania. Therefore, if hypomania is frequent, severe, or impairing, clinicians should consider classic mood-stabilizing medications, such as lithium or divalproex, and/or atypical antipsychotics.

Acute Management of Bipolar II Depression

First-, second-, and third-line treatment options for bipolar II depression are listed in Box 4. Quetiapine is the only recommended first-line treatment for bipolar II depression. Second-line options include lithium, ideally at a serum level of 0.8–1.2 mEq/L, and the antidepressants sertraline and venlafaxine, mainly for patients with pure (nonmixed) depression. Lamotrigine is also recommended as a second-line agent. ECT is considered as a second-line option, especially for patients with treatment-refractory bipolar II depression and those who require rapid response.

Update on Studies Showing Efficacy of Drugs in Bipolar II Depression

As mentioned earlier, a recent RCT (Level 2) showed the efficacy of 42 mg lumateperone in the treatment of bipolar I and bipolar II depression (27). Given that the data for bipolar II depression was based on a small number of patients and, furthermore, that there is only limited clinical experience with lumateperone in this population, we recommend it as a second-line option for the treatment of acute bipolar II depression.

Maintenance Treatment of Bipolar II Disorder

Maintenance treatment is important to prevent relapse and restore functioning and quality of life. Selection of an agent for maintenance should be informed by acute-phase treatment. First-, second-, and third-line treatment options are listed in Box 4.

Quetiapine, lithium, and lamotrigine monotherapies are first-line options, whereas venlafaxine and fluoxetine are considered second-line options.

MANAGEMENT OF BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS

Presentation and Diagnosis

Between one-third and two-thirds of individuals with bipolar disorder experience their first mood episode during childhood or adolescence. Despite developmental differences in the way symptoms manifest themselves, the diagnosis of bipolar disorder in children and adolescents should be made on the basis of the same criteria used in adults (31). It is important for clinicians to distinguish between discrete periods of elevated or irritable mood that are characteristic of manic or hypomanic episodes and chronic irritability with episodic behavioral outbursts that can be seen in other conditions such as emerging personality disorders, substance use disorder, and ADHD. When defined according to *DSM-5* criteria, the course of bipolar disorder in youths tends to be characterized by high rates of symptomatic recovery but also high rates of recurrence (32).

Pharmacological Management

Readers should consult the 2018 guideline document for more detailed information about the rationale for recommended treatment options.

Acute mania. Lithium, risperidone, aripiprazole, asenapine, and quetiapine are recommended as first-line options. Olanzapine and ziprasidone monotherapy and quetiapine adjunctive therapy are recommended as second-line options, whereas divalproex is considered a third-line treatment.

Acute depression. Lurasidone is recommended as the only first-line treatment. Lithium and lamotrigine are recommended as second-line options, whereas an olanzapine-fluoxetine combination and quetiapine are recommended as third-line options. Antidepressants should be used with caution and only in combination with mood-stabilizing medications in youths with bipolar depression.

Maintenance treatment. First-line maintenance treatment options are aripiprazole, lithium, and divalproex. Although the 2018 CANMAT/ISBD guideline does not recommend any second-line maintenance option in this population, asenapine, quetiapine, risperidone, and ziprasidone are recommended as third-line options.

Treatment of comorbid conditions. Psychostimulants can be used to treat comorbid ADHD in youths in a euthymic phase of bipolar disorder who are taking optimal doses of antimanic medications. Comorbid substance use disorder should be treated concurrently with mood symptoms. Lithium may be effective for reducing substance use in youths diagnosed as having bipolar disorder (33).

MANAGEMENT OF BIPOLAR DISORDER IN OLDER AGE

Presentation and Course

In 2005, about 25% of the patients with bipolar disorder in the United States were over 60 years old (34), and by 2030, over half of all patients with bipolar disorder are expected to be older than 60 years of age (35). The lifetime prevalence of late-life bipolar disorder is between 1% and 2% in the general population. About 90%–95% of older adults with bipolar disorder experience their first mood episode before age 50, whereas there is a minority who will have a later onset (36, 37). Late onset is often related to neurological or physical comorbidity (38) and might indicate poor prognosis (39).

Manic symptoms tend to be less prominent in this population, but depressive and cognitive symptoms are more often observed (40). Cognitive impairment is a major concern, with over 30% showing significant deficits across all cognitive domains, even during euthymia (41, 42).

Psychiatric comorbidity is less prevalent than in younger patients, with anxiety and substance use disorder being the most common (37). In addition, older adults with bipolar disorder have an average of three to four comorbid medical conditions (43) that contribute to a life expectancy reduction of 10–15 years with bipolar disorder, compared with nonpsychiatric populations (44). Assessment of an older adult with bipolar disorder should include a thorough physical and neurological examination, as well as clinical laboratory tests. Neuroimaging should also be considered particularly if there are focal neurological signs and symptoms; if there is an abrupt, late onset; or if the presentation is different from previous episodes.

Pharmacological Treatment

Acute mania. Lithium and divalproex are recommended as first-line treatment options, whereas quetiapine can be considered as a second-line treatment option. Asenapine, aripiprazole, risperidone, and carbamazepine are recommended as third-line treatment options. Clozapine and ECT should be considered for treatment-resistant episodes.

Acute depression. Quetiapine and lurasidone monotherapy are recommended as first-line options. However, given the concerns regarding the side effects of atypical antipsychotics in this population, clinicians may choose to try lithium or lamotrigine first. Divalproex, aripiprazole, and carbamazepine are third-line options, and ECT should be considered as an option for treatment-resistant depression, for suicidal patients, and for patients with inadequate food or fluid intake. Antidepressants such as SSRIs and bupropion can be used in combination with mood stabilizers in selected patients who cannot tolerate or do not respond to other treatments.

Maintenance treatment. Treatment choice for maintenance should be based on what has been effective in the acute phase, with recommended options with efficacy data in older adults being lithium, lamotrigine, and divalproex.

SAFETY AND MONITORING

Medical Evaluation and Laboratory Investigations

A complete medical history as well as assessment of body mass index and laboratory investigations should be performed prior to initiating pharmacological treatment for bipolar disorder or as soon as the patient is cooperative. Baseline laboratory investigations include complete blood count, fasting glucose, fasting lipid profile, electrolytes, and calcium; liver enzymes; serum bilirubin; prothrombin time and partial thromboplastin time; urinalysis; urine toxicology for substance use; serum creatinine and estimated glomerular filtration rate; thyroid-stimulating hormone; electrocardiogram (for patients over 40 years of age or if otherwise indicated); pregnancy test; and serum prolactin. In individuals of childbearing potential, pregnancy should be ruled out, and consultation should be provided regarding the possibility of lamotrigine and carbamazepine affecting the efficacy of oral contraceptives. For patients who are on lithium, thyroid and renal function as well as plasma calcium should be assessed at baseline, after 6 months, and at

least annually thereafter. In patients who are on divalproex, menstrual history (to assess for polycystic ovary syndrome), hematology profile, and liver function tests should be obtained at 3- to 6-month intervals during the first year and yearly thereafter. Health Canada warns "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" (45). Patients initiated on lamotrigine or carbamazepine should receive education regarding the risks of skin rashes and the potential for Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, those who are on carbamazepine should have serum sodium levels measured at least annually because of the risk of hyponatremia. Patients on atypical antipsychotics should have their body weight monitored monthly in the first 3 months and every 3 months thereafter. In addition, blood pressure, fasting glucose, and lipid profile should be assessed at 3 months and yearly thereafter. Regular monitoring for extrapyramidal symptoms is also recommended.

Monitoring Medication Serum Levels

Lithium, divalproex, and carbamazepine serum levels need to be monitored regularly. Measurement of serum levels should be done at the trough point, which is 12 hours after the last dose. Two consecutive serum levels in the therapeutic range should be established after the initiation of lithium and divalproex, and then measurement should be repeated at least every 3–6 months. Carbamazepine levels may be monitored every 6–12 months and as clinically indicated. Target serum level for lithium is 0.8–1.2 mEq/L (0.4–0.8 mEq/L in older adults) in the acute phase and 0.6–1 mEq/L during maintenance. Serum levels should be checked at least 5 days after the most recent dose titration. The target serum level for divalproex is 350–700 mM/L (50–100 μg/mL) and should be checked at least 3–5 days after the most recent dose titration.

CONCLUSIONS

The assessment and treatment of bipolar disorder can be a challenge for clinicians, given its clinical complexity and the growing range of treatment options available for various phases of the illness. This article provides a summary of the 2018 CANMAT/ISBD guideline recommendations for the treatment of bipolar disorder across the lifespan and incorporates updates from studies published in the past 5 years, with the aim of aiding clinicians in delivering evidence-based care to their patients.

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