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BIPOLAR DISORDERS

Guidelines Update

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009

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The Canadian Network for Mood and Anxiety Treatments (CANMAT) published guidelines for the management of bipolar disorder in 2005, with a 2007 update. This second update, in conjunction with the International Society for Bipolar Disorders (ISBD), reviews new evidence and is designed to be used in conjunction with the previous publications.

The recommendations for the management of acute mania remain mostly unchanged. Lithium, valproate, and several atypical antipsychotics continue to be first-line treatments for acute mania. Tamoxifen is now suggested as a third-line augmentation option. The combination of olanzapine and carbamazepine is not recommended. For the management of bipolar depression, lithium, lamotrigine, and quetiapine monotherapy, olanzapine plus selective serotonin reuptake inhibitor (SSRI), and lithium or divalproex plus SSRI/bupropion remain first-line options. New data support the use of adjunctive modafinil as a second-line option, but also indicate that aripiprazole should not be used as monotherapy for bipolar depression. Lithium, lamotrigine, valproate, and olanzapine continue to be first-line options for maintenance treatment of bipolar disorder. New data support the use of quetiapine monotherapy and adjunctive therapy for the prevention of manic and depressive events, aripiprazole monotherapy for the prevention of manic events, and risperidone long-acting injection monotherapy and adjunctive therapy, and adjunctive ziprasidone for the prevention of mood events.

Bipolar II disorder is frequently overlooked in treatment guidelines, but has an important clinical impact on patients' lives. This update provides an expanded look at bipolar II disorder.

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The authors dedicate the CANMAT/ISBD guidelines to Dr. Vivek Kusumakar, who passed away suddenly on January 14, 2009. He was an editor for the first CANMAT Guidelines for bipolar disorder, published in 1997. Dr. Kusumakar's intellectual curiosity to understand the causes of mental illnesses, scientific ability to lead discovery and development of new treatments, develop and disseminate innovative educational programs to improve outcomes for people with bipolar disorder, and his drive for excellence, along with an ability to inject his vision and enthusiasm to his colleagues will be sorely missed.

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Section 1. Introduction

In 2005, the Canadian Network for Mood and Anxiety Treatments (CANMAT) published revised guidelines for the management of bipolar disorder (BD) (1), followed by a 2007 update (2). The current update is the result of a collaborative effort between the CANMAT group and the International Society for Bipolar Disorders (ISBD). The update includes data published since 2007, and is designed to be used in conjunction with the 2005 CANMAT Guidelines and previous update (1, 2).

Search strategies and methods to assess evidence were as described in the original guidelines (1). Evidence available only in abstract form was also considered, in order to ensure that the recommendations are as up to date as possible. The criteria for rating strength of evidence and making a clinical recommendation are shown in Tables 1.1 and 1.2.

The purpose of this update is to add previously unpublished material to the guidelines and to expand the discussion of bipolar II disorder (BD II). Our goal is to ensure that the CANMAT guidelines for treatment of BD remain current and useful for the practicing clinician.

Section 2. Foundations of management

Epidemiology

Prevalence. The U.S. National Comorbidity Survey Replication (n = 9,282) published in 2007 reported lifetime (and 12-month) prevalence estimates of 1.0% (0.6%) for BD I, 1.1% (0.8%) for BD II, and 2.4% (1.4%) for subthreshold BD (defined as recurrent hypomania without a major depressive episode or with fewer symptoms than required for threshold hypomania) (3). Most respondents had lifetime comorbidity with other Axis I disorders, particularly anxiety disorders. As expected, clinical severity and role impairment were greater for threshold than for subthreshold BD. In addition, severity and role impairment during major depressive episodes were greater in BD II compared to BD I, while subthreshold cases still had moderate to severe clinical severity and role impairment.

Table 1.1. Evidence criteria

1	Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo condition
2	At least one DB-RCT with placebo or active comparison condition
3	Prospective uncontrolled trial with at least 10 or more subjects
4	Anecdotal reports or expert opinion

Table 1.2. Treatment recommendation

First line	Level 1 or Level 2 evidence plus clinical support for efficacy and safety
Second line	Level 3 evidence or higher plus clinical support for efficacy and safety
Third line	Level 4 evidence or higher plus clinical support for efficacy and safety
Not recommended	Level 1 or Level 2 evidence for lack of efficacy

Diagnostic assessment

The ISBD Diagnostic Guidelines Task Force suggested revisions that should be included in the DSM-V and ICD-11 for bipolar disorders (4). These are summarized here, but please refer to the ISBD Diagnostic Guidelines Task Force Report for more information (4). For BD I, the ISBD suggested that the DSM-IV criteria for mania remain unchanged, but that the criteria for bipolar depression should include a probabilistic approach that takes into account the presence of (i) atypical depressive symptoms (hypersomnia, hyperphagia, or leaden paralysis), (ii) psychomotor disturbance, (iii) psychotic features or pathological guilt, and (iv) a positive family history of bipolar disorder. In addition, the rapid cycling specifier should be applicable to BD not otherwise specified (NOS), as well as BD I and BD II. The ISBD also suggested changes to the diagnostic criteria for BD II, which are discussed in section 7.

The ISBD suggested increasing recognition of bipolar spectrum disorders through expansion of the definitions of BD NOS, adding the following: subthreshold hypomanic episodes in the context of multiple other signs of bipolarity, and multiple signs of bipolarity without hypomanic or manic episodes (also known as bipolar spectrum disorder). Signs of bipolarity include: family history (BD, mental illnesses, alcohol/substance use, suicides), depressive symptoms (atypical, seasonal, psychomotor slowing, psychosis), and course of illness (early age of onset, short duration of episodes, greater number of episodes). The ISBD also suggested the addition of operational criteria for schizoaffective disorders and childhood-onset BD.

Several studies suggest the temporal instability of a bipolar diagnosis and the need for multiple

visits to confirm the diagnosis in some patients. While misdiagnosis of BD as major depressive disorder (MDD) is common (5, 6), overdiagnosis of BD may also occur (7). Data from a registry analysis support that the initial course of BD causes difficulties in the diagnosis, with a high proportion of over- and underdiagnosis of BD (7).

Differentiating MDD and BD, particularly BD II, can be a challenge. Several studies have found that BD is associated with a significantly earlier age of onset, more recurrences, atypical and mixed depressions, and family history of BD or completed suicide compared to MDD (6, 8). Mixed states are highly predictive of a BD diagnosis, especially BD II (5, 8). In addition, mixed states have been associated with an increased lifetime risk for comorbid psychiatric disorders, more mood episodes, higher rates of treatment contacts, and lower rates of full-time employment compared to pure states (9).

Psychosocial interventions

When used adjunctively to pharmacotherapy, psychosocial interventions such as group psychoeducation, cognitive behaviour therapy (CBT), and interpersonal and social rhythm therapy (IPSRT) have each demonstrated a number of significant benefits, such as decreased relapse rates, mood fluctuations, need for medications, and hospitalizations, as well as increased functioning and medication adherence [see 2005 guidelines for review (1)]. Therefore, providing psychoeducation is an especially essential part of management of patients with BD.

A review of bipolar guideline implementation projects concluded that recommendations requiring little change to working practices and resources are most likely to be implemented (10). Psychological interventions are difficult to implement because of shortages of skilled staff, absence of specific training and supervision, requirements for staff to adopt techniques that are quite different from usual practice, and uncertainty about whether these interventions are effective in the most severe patients. However, it must be remembered that most therapies studied have shown benefit as adjuncts to pharmacotherapy with no substantial differences between the treatments in efficacy. In light of this, and given that simple psychoeducation can be offered by any clinician, this should be the essential component of clinical management of BD for all patients. Internet-based interventions are also becoming available which may assist the capacity constraints of psychosocial treatments.

Section 3. Acute management of bipolar mania

Emergency management of agitation

There are randomized controlled trial (RCT) data to support the use of IM aripiprazole, which can now be considered as a first choice in the treatment of acute agitation (Level 2) (11). In a large RCT (n = 301), IM aripiprazole was as effective as IM lorazepam and more effective than IM placebo within 45–60 minutes for the treatment of agitation in patients with BD I manic or mixed episodes.

Additional data support the use of IM olanzapine for severely agitated inpatients with acute mania. In a one-week, observational study, patients exhibited mild calmness and significantly reduced agitation within two hours of administration of IM olanzapine (12). Over 90% of the patients received only one injection in the first 24 hours and 50% had a categorical response within 30 minutes.

Pharmacological treatment of manic episodes

Overall, treatment strategies for the pharmacological management of acute manic episodes remain mainly unchanged (see Fig. 3.1) (1, 2). Several meta-analyses have helped to clarify the efficacy of recommended treatments (Table 3.3). In addition, adjunctive aripiprazole can now be recommended as a first-line option. Asenapine, alone or in combination with lithium or divalproex, as well as paliperidone as monotherapy but not as adjunctive therapy have been added as second-line options.

Step 1. Review general principles and assess medication status: Recommendations from 2005 guidelines remain unchanged.

Step 2. First-line therapies: Two meta-analyses confirm the efficacy of antipsychotics, lithium and divalproex for the treatment of acute mania (13, 14). A meta-analysis of 13 RCTs (n = 3,089) found that carbamazepine, haloperidol, lithium, olanzapine, quetiapine, risperidone, divalproex, and aripiprazole showed significant benefit compared with placebo for reduction in mania scores (13). Response rates were 1.7 times [risk ratio (RR) 1.74) greater for all antipsychotics pooled, and doubled (RR 2.01) for lithium/divalproex pooled, compared to placebo. There were no differences in effect sizes between the various antimanic treatments. A meta-analysis of 24 studies (n = 6,187)

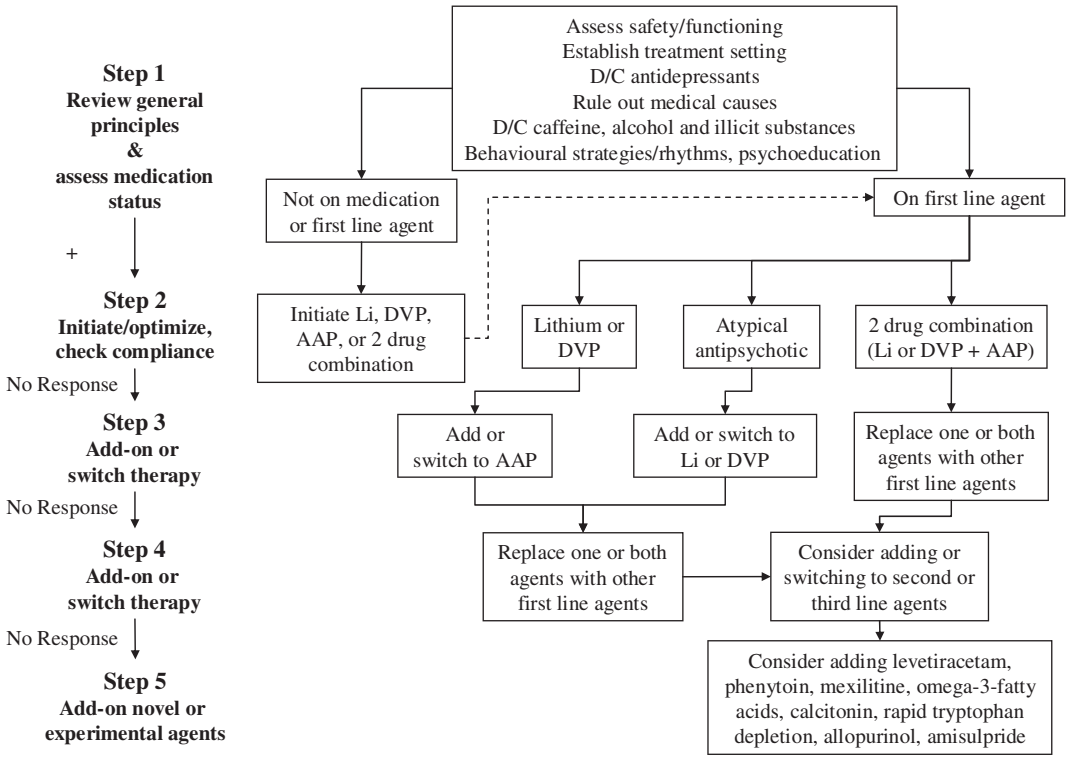

Fig. 3.1. Treatment algorithm for acute mania.
D/C = discontinue; Li = lithium; DVP = divalproex; AAP = atypical antipsychotic.

found that atypical antipsychotics were significantly more efficacious than placebo (12 studies), and as effective as lithium/divalproex (five studies) (14). Some atypical antipsychotics seemed to have higher rates of extrapyramidal symptoms and somnolence than placebo.

Atypical antipsychotic monotherapy. Substantial RCT data support the efficacy of atypical antipsychotic monotherapy with olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole for the first-line treatment of acute mania (Level 1) (1, 2).

A four-week RCT conducted in China suggested that olanzapine was significantly more effective than lithium in the acute treatment of 140 BD patients with a manic or mixed episode (15). The incidence of adverse events, including weight gain, was greater with olanzapine.

A Cochrane database systematic review, including six trials (n = 1,343) of risperidone as monotherapy or as adjunct to lithium or an anticonvulsant for the treatment of acute mania, confirmed that risperidone was more effective than placebo and as effective as haloperidol (Level 1) (16).

A three-week RCT (n = 329) found that olanzapine and risperidone were equally effective on most measures of manic and depressive symptoms (17).

As reported in the 2005 guidelines, five studies have demonstrated the efficacy of quetiapine as monotherapy (18, 19) or in combination with lithium/divalproex (20–22) in the treatment of acute mania, and several reviews and pooled

Table 3.3. Recommendations for pharmacological treatment of acute mania

First line	Lithium, divalproex, olanzapine, risperidone, quetiapine, ***quetiapine XR***[a], aripiprazole, ziprasidone, lithium or divalproex + risperidone, lithium or divalproex + quetiapine, lithium or divalproex + olanzapine, ***lithium or divalproex + aripiprazole***[a]
Second line	Carbamazepine, ECT, lithium + divalproex, ***asenapine***[a], ***lithium or divalproex + asenapine***[a], ***paliperidone monotherapy***[a]
Third line	Haloperidol, chlorpromazine, lithium or divalproex + haloperidol, lithium + carbamazepine, clozapine, ***oxcarbazepine***[a], ***tamoxifen***[a]
Not recommended	Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, risperidone + carbamazepine, ***olanzapine + carbamazepine***[a]

ECT = electroconvulsive therapy.
[a]**New**.

analyses have further explored the results of these trials (23–28). A pooled analysis of the two monotherapy RCTs (n = 403) reported significantly higher remission rates with quetiapine at three weeks and 12 weeks compared to placebo (23). Similarly, a pooled analysis of two adjunctive therapy RCTs (n = 370) found significantly higher remission rates with adjunctive quetiapine at three weeks compared to lithium/divalproex alone (24). In addition, reviews of these data have confirmed that the efficacy of quetiapine was superior to placebo and at least comparable to lithium and haloperidol (25). Quetiapine was well tolerated, with most adverse events being mild to moderate and discontinuations for adverse events not being significantly different from placebo (26). Finally, the efficacy of quetiapine appeared to be independent of baseline disease severity, the presence of psychosis, and treatment-emergent sedation/somnolence (28).

Data from a three-week RCT of quetiapine XR in patients with BD I manic or mixed episode have been presented in abstract form (29). Quetiapine XR monotherapy significantly improved manic symptoms starting at day 4.

As reported in the 2005 guidelines, three studies have demonstrated the efficacy of aripiprazole monotherapy compared to placebo (30, 31) or haloperidol (32) in the treatment of acute mania. While no new data are available, several pooled analyses provide additional support for these placebo-controlled trials (33, 34). Aripiprazole was effective in patients with more or less severe illness, mixed or manic episodes, with or without psychotic features, and with a history of rapid or non-rapid cycling; in men and women; in younger and older patients; in those with more or less severe depressive symptoms (33); and in those with or without agitation (34). One RCT assessed the role of adjunctive aripiprazole (discussed below in combination therapy) (35).

Pooled analysis of two previously reported RCTs showed that partial response to ziprasidone treatment as of day 2 was predictive of a later full response (36).

Ziprasidone has recently become available in Canada, while aripiprazole continues to be unavailable, so recommendations are based largely on the reported efficacy data and adverse event profile of these agents.

Combination therapy. Two meta-analyses have confirmed the efficacy of combination therapy with antipsychotics plus lithium/divalproex (Level 1) (14, 37). A meta-analysis of eight studies (n = 1,124) found significant reductions in mania scores with adjunctive haloperidol, olanzapine, risperidone, and quetiapine compared with lithium/divalproex alone (37). For adjunctive atypical antipsychotics combined, the pooled difference in mean scores was 4.41. Response rates were significantly higher with combination therapy (RR 1.53) compared with lithium/divalproex alone. A meta-analysis of 24 studies (n = 6,187), found that adding atypical antipsychotic agents to lithium/divalproex was significantly more effective than treatment with lithium/divalproex alone (six studies) for the treatment of acute mania (14).

A six-week, placebo-controlled RCT showed that aripiprazole added to therapy in 384 patients with inadequate response to lithium or divalproex was significantly more effective than placebo from week 1 on (35). At six weeks, response and remission rates were significantly higher with aripiprazole than placebo.

Step 3. Add-on or switch therapy (alternate first-line therapies): No changes from 2005 guidelines.

Step 4. Add-on or switch therapy (second- and third-line therapies):

Second-line options. Paliperidone is approved for the treatment of schizophrenia but has not yet been approved for the treatment of bipolar disorder. Results from two three-week, double-blind RCTs in patients with BD manic or mixed episodes have been reported; one fixed- and one flexible-dose trial (Level 1) (38, 39). Flexible-dose paliperidone (n = 190, mean dose 9 mg/day) was more effective than placebo (n = 104) in improving manic symptoms as early as day 2 (38). In the fixed-dose study, paliperidone 12 mg/day (n = 115), but not 3 mg/day (n = 112) or 6 mg/day (n = 119), was more effective than placebo (n = 121) in patients hospitalized for at least the first seven days of treatment (39). Because of the lack of clinical experience with this agent, paliperidone monotherapy is recommended as a second-line option, based on the reported efficacy data and adverse event profile of this agent.

Although not yet approved in Canada or the United States, asenapine may be a promising agent for the management of mania. Two similar three-week, double-blind RCTs with a total of 976 patients demonstrated that asenapine and olanzapine were significantly more effective than placebo (Level 1) (40–42). Efficacy was maintained in 504 patients during a nine-week, double-blind extension phase, and in 218 patients continuing a 40-week extension study, with no significant differences between asenapine and olanzapine in these extension studies.

A 12-week RCT of adjunctive asenapine or placebo compared to lithium/divalproex in 318 patients with BD manic or mixed episodes found significant improvements in mania symptoms in the active augmentation group compared to placebo (Level 2) (43).

Despite clinical trial evidence, clinical experience is lacking; therefore, asenapine alone or in combination with lithium or divalproex is recommended as a second-line option, based on the reported efficacy data and adverse event profile of this agent.

Third-line options. A Cochrane Database review confirming the efficacy of haloperidol for mania included 15 trials (n = 2,022) (Level 1) (44). Haloperidol, both as monotherapy and adjunct to lithium or divalproex, was more effective than placebo at reducing mania symptoms. Haloperidol was as effective as olanzapine, risperidone, carbamazepine, or divalproex. Haloperidol was associated with less weight gain than olanzapine, but with a higher incidence of tremor and other movement disorders. Given the high rates of movement disorders, as well as the potential for increased risk of switch into depressive episodes, haloperidol continues to be recommended as a third-line option.

There are now four small RCTs assessing tamoxifen in patients with BD, two as monotherapy (three weeks' duration; n = 66 and n = 16) (Level 2) (45, 46) and two as adjunct to lithium/divalproex (four weeks' duration; n = 43 and n = 13) (Level 2) (47, 48). In all the studies, tamoxifen was associated with significant improvement in manic symptoms. However, only one of these four trials had a sample size of 30 patients or more per group. Therefore, given the small sample sizes, limited experience, and side effects in BD mania with this agent, tamoxifen is currently recommended as a third-line option.

Oxcarbazepine was previously recommended as a second-line option based on data from several very small RCTs (Level 2) (1). However, a recent seven-week RCT in 116 youths with BD I manic or mixed episode found no significant improvement in mania symptoms with oxcarbazepine compared to placebo (Level 2, negative) (49). In light of this negative trial, and clinical experience, oxcarbazepine has been moved to a third-line option.

Step 5. Add-on novel or experimental agents: In a small RCT in 23 patients with acute mania, there was greater improvement in mania ratings in patients receiving adjunctive rapid tryptophan depletion, through administration of an oral tryptophan-free amino acid solution, compared to placebo (Level 2) (50). Allopurinol as adjunct to lithium plus haloperidol was found to be significantly more effective than placebo in an eight-week RCT in 82 patients hospitalized with acute mania (Level 2) (51). However, given the very limited data, these agents can only be recommended as add-on therapies after failure of all standard therapies.

Adjunctive amisulpride was as effective as adjunctive haloperidol when added to divalproex therapy in 123 patients with BD I in a 12-week, randomized, open-label trial (Level 3) (52). Response rates were 72.6% in the amisulpride group and 65.5% in the haloperidol group, with no significant difference between groups.

Not recommended for acute mania: There were no significant differences in efficacy between combined olanzapine plus carbamazepine compared to carbamazepine alone in 118 patients with manic or mixed BD episodes (Level 2, negative) (53). In light of the fact that the combination was associated with significantly higher rates of lipid abnormalities and weight gain, the combination is not recommended.

A six-week RCT assessing the efficacy of adjunctive flexible-dose paliperidone or placebo in 300 patients with BD manic or mixed episodes that were uncontrolled on lithium or divalproex found no significant improvements in mania symptoms (Level 2, negative) (54). Given that paliperidone monotherapy is effective and given that lithium or valproate does not affect the metabolism of paliperidone, the lack of efficacy of combination therapy is surprising. The details of this study are currently available only in abstract form, and based on the available information, it would appear that paliperidone may have been underdosed, as the mean dose was only 8 mg/day, while the monotherapy studies suggest that 12 mg/day is the most effective dose. Therefore, at this time, adjunctive paliperidone should be tried only when other antipsychotic augmentation strategies have failed.

Clinical features that can help direct treatment choices

A post hoc analysis of one RCT trial (n = 332) comparing olanzapine and haloperidol found that Caucasian patients had higher remission rates with olanzapine compared to haloperidol, whereas Latin American patients experienced similar remission rates with both treatments (55). Please refer to the 2005 guidelines for a detailed list of other predictors of response. Although many agents are

of broadly comparable efficacy, tolerability issues are important in guiding treatment choice, given that acute treatment frequently becomes long-term treatment.

Section 4. Acute management of bipolar depression

Psychosocial interventions for depressive episodes

In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial, 293 patients with BD I or BD II depression were randomized to receive intensive psychotherapy (n = 163) or collaborative care (n = 130), i.e., a brief psychoeducational intervention as an adjunct to pharmacotherapy (56). Intensive psychotherapy included family-focused therapy (FFT), IPSRT, and CBT weekly and biweekly for up to 30 sessions in nine months, and collaborative care consisted of three sessions in six weeks. Discontinuation rates were similar with both treatments. Patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64.4% versus 51.5%) and shorter times to recovery than patients in collaborative care. There were no statistically significant differences between the three types of intensive psychotherapies. In a subsequent report of 152 patients from this study, intensive psychotherapy was associated with better total functioning, relationship functioning, and life satisfaction scores but not work/role functioning or recreation scores over nine months compared to collaborative care (57).

Pharmacological treatment of depressive episodes

Pharmacological management of acute depressive episodes should follow the algorithm outlined in Fig. 4.1 (1). A number of new clinical trials in bipolar depression justify additions to the treatment recommendations for bipolar depression (Table 4.3). First-line options have not changed from the 2007 guideline update (2), but the evidence for quetiapine monotherapy as a first-line option has been strengthened. Divalproex monotherapy and adjunctive modafinil have been added as second-line options, and two negative trials for

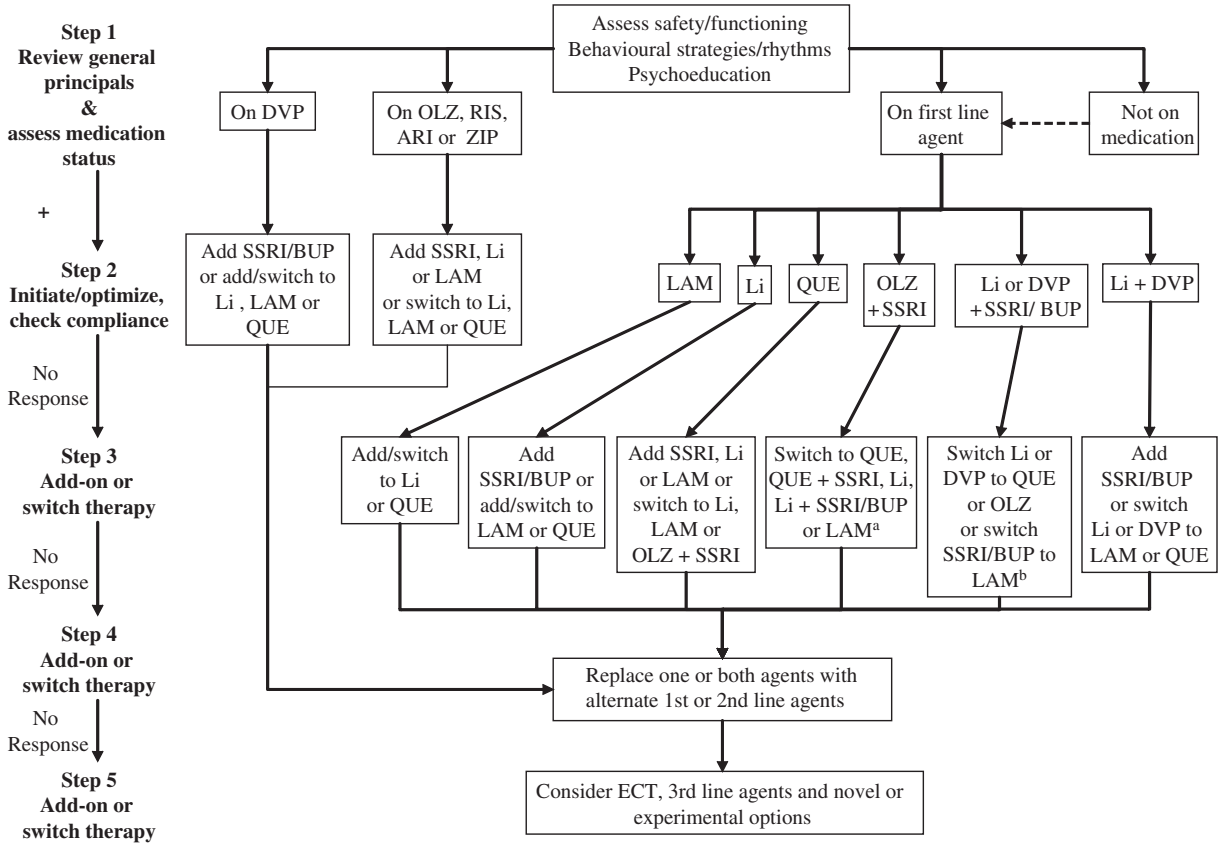

Fig. 4.1. Treatment algorithm for the management of bipolar I depression.
DVP = divalproex; OLZ = olanzapine; RIS = risperidone; ARI = aripiprazole; ZIP = ziprasidone; SSRI = selective serotonin reuptake inhibitor; BUP = bupropion; Li = lithium; LAM = lamotrigine; QUE = quetiapine; ECT = electroconvulsive therapy.
[a]Or switch the SSRI to another SSRI.
[b]Or switch the SSRI or BUP to another SSRI or BUP.

Table 4.3. Recommendations for pharmacological treatment of acute bipolar I depression[a]

First line	Lithium, lamotrigine, quetiapine, ***quetiapine XR***[b], lithium or divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion
Second line	Quetiapine + SSRI, ***divalproex***[b], lithium or divalproex + lamotrigine, ***adjunctive modafinil***[b]
Third line	Carbamazepine, olanzapine, lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, ECT, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI + lamotrigine, adjunctive EPA, adjunctive riluzole, adjunctive topiramate
Not recommended	Gabapentin monotherapy, ***aripiprazole monotherapy***[b]

SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; ECT = electroconvulsive therapy; AAP = atypical antipsychotic; TCA = tricyclic antidepressant; EPA = eicosapentaenoic acid.

[a]The management of a bipolar depressive episode with antidepressants remains complex. The clinician must balance the desired effect of remission with the undesired effect of switching.

[b]**New**.

aripiprazole led to a recommendation against using aripiprazole monotherapy for the acute management of bipolar depression.

Step 1. Review general principles and assess medication status: Recommendations from 2005 guidelines remain unchanged.

Step 2. Initiate or optimize therapy and check adherence (first-line therapies): Lithium, lamotrigine, lithium or divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion, and quetiapine monotherapy continue to be recommended as first-line choices for bipolar depression.

Lamotrigine. Lamotrigine was recommended for the acute treatment of bipolar depression based on two positive RCTs (Level 1), one large parallel-group trial (58), and a small crossover trial (59). Calabrese et al. (60) reviewed the results of five double-blind, placebo-controlled RCTs: the published large RCT and four other previously unpublished trials. There were about 200 patients in each of these five trials for a total of over 1,000 patients. Lamotrigine monotherapy did not demonstrate efficacy in the acute treatment of bipolar depression in 4 out of 5 RCTs in terms of change in the primary efficacy endpoints [change in 17-item Hamilton Depression Rating Scale (HAM-D) or Montgomery–Åsberg Depression Rating Scale (MADRS) scores]. The lack of significant differences may be due to the large placebo response rate in these four studies. However, a meta-analysis of individual patient data from all five RCTs did show that patients treated with lamotrigine were significantly more likely to respond (> 50% reduction in score on the HAM-D or MADRS) than those treated with placebo (Level 1, positive) (61). The remission rates were significant on the MADRS but not on the HAM-D. Similarly, the depressive symptom change scores were greater with lamotrigine on the MADRS but not on the HAM-D. Taken together, these data suggest that lamotrigine has modest antidepressant efficacy in monotherapy and that the individual trials were likely underpowered to capture the benefits of lamotrigine.

These data and a wealth of clinical experience with this compound led the committee to continue to recommend lamotrigine as a first-line treatment option. However, clinicians should discuss with patients the risk of skin rash, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis, carefully follow titration guidelines, and monitor for occurrence of these events.

Quetiapine monotherapy. There are now four large RCTs demonstrating the efficacy of quetiapine monotherapy in bipolar depression; BOLDER I (62) and II (63), which were cited in previous iterations of these guidelines; and two additional eight-week RCTs, EMBOLDEN I (64) and EMBOLDEN II (65), which have now been reported in abstract form (Level 1). EMBOLDEN I compared quetiapine and lithium in 802 patients with bipolar depression, and EMBOLDEN II compared quetiapine and paroxetine in 740 patients. In EMBOLDEN I, quetiapine (300 or 600 mg/d) was significantly more effective than placebo on the primary efficacy measure of change in MADRS scores as well as response and remission rates, but lithium was not (64). However, the mean serum lithium level in this study was only 0.6 meq/L, which may not have been therapeutic for alleviating depressive symptoms. A subanalysis of data for those who had serum levels of 0.8 meq/L or above is awaited. In EMBOLDEN II, the improvement in MADRS scores and response rates for quetiapine (both doses) was significantly greater than placebo, but paroxetine was not more effective than placebo (65). Remission rates were significantly greater with quetiapine 600 mg/d, but not quetiapine 300 mg/d compared with placebo; a similar proportion of placebo and paroxetine-treated patients achieved remission. It is unclear if a higher dose of paroxetine (greater than 20 mg/d) would have

been effective, as patients in this study were treated with a fixed dose of 20 mg/d. Both trials also showed significant improvements in MADRS item 10 (suicidal thoughts) with quetiapine versus placebo.

Data from an eight-week RCT assessing quetiapine XR in 270 patients with BD I or BD II depression have been presented in abstract form (66). Quetiapine XR monotherapy showed significantly greater improvement in depressive symptoms from week 1, which was maintained to study end.

Lithium or divalproex + bupropion or paroxetine. In the STEP-BD study, lithium/divalproex plus an adjunctive antidepressant (bupropion or paroxetine) was no more effective than lithium/divalproex plus placebo for up to 26 weeks in 366 patients with bipolar depression (67). Rates of durable recovery (eight consecutive weeks of euthymia) were comparable for adjunctive antidepressants and lithium/divalproex alone ($p = 0.4$). Adjunctive antidepressant therapy was not associated with increased risk of treatment-emergent affective switch. However, adjunctive antidepressant use was associated with significantly higher mania symptom ratings at the three-month follow-up visit (68). Since patients for this trial were recruited primarily from tertiary-care specialized mood disorders centers, the data may not be generalizable to all bipolar depressed patients. In addition, the primary outcome in this study was different than the outcome used in other studies, and the results of traditional outcomes such as MADRS change scores at week 6 or week 8 are awaited. Given the challenges in demonstrating the efficacy of various agents for treating bipolar depressive symptoms, it might be worth examining the sensitivity of current rating instruments in detecting clinically meaningful differences between active agents and placebo. In any event, given that antidepressants are widely used in clinical practice to treat bipolar depression, further trials assessing their efficacy are required.

Step 3. Add-on or switch therapy (alternate first- or second-line therapies): No changes from 2007 guideline update.

Step 4. Add-on or switch therapy (alternate first- or second-line therapies):

Adjunctive modafinil. In a six-week RCT, adjunctive modafinil was significantly better than placebo in improving depressive symptoms in 85 patients with bipolar depression who had not responded to lithium/divalproex with or without concomitant antidepressants (Level 2) (69). There was no difference between groups in treatment-emergent hypomania or mania. A retrospective chart review of patients receiving modafinil ($n = 66$) found that no patients in any group demonstrated switch into mania or hypomania while on modafinil (70). Modafinil has a high potential for interactions with drugs from all classes and can cause serious dermatological reactions, particularly when used at higher doses (71).

Modafinil may be a useful adjunctive therapy that does not appear to have a manic switch liability. However, because of safety concerns and limited experience with this agent in patients with BD, it is recommended as a second-line option and should be used with caution and careful patient monitoring.

Divalproex monotherapy. There are now three small RCTs assessing the efficacy of divalproex or divalproex ER for the treatment of patients with BD I or II depression (Level 1) (72–74). In all three studies, divalproex was associated with significant improvements in depressive symptoms. However, none of these trials had a sample size of 30 patients or more per group. Therefore, given the small sample sizes, divalproex is currently recommended as a second-line option.

Step 5. Add-on or switch therapy (third-line agents and novel/experimental therapies):

Third line. A small, open, randomized trial provided additional support for adjunctive use of the monoamine oxidase inhibitor tranylcypromine (Level 3) (75). During 10 weeks of treatment, 5/8 patients (62.5%) responded to tranylcypromine without switch into mania, compared with 4/11 patients (36.4%) on lamotrigine with two switches (not statistically significant).

Novel or experimental agents. In a 24-week RCT, adjunctive N-acetyl cysteine significantly improved depressive symptoms in 75 patients with BD in the maintenance phase (about 50% of patients were euthymic) (Level 2) (76).

Agents not recommended for the treatment of acute bipolar depression:

Aripiprazole monotherapy. In a report of two identically designed, eight-week, multicenter, double-blind RCTs, aripiprazole (5–30 mg/d) monotherapy was no more effective than placebo in 749 patients with bipolar depression and was associated with higher incidence of side effects and higher discontinuation rates than placebo (Level 1, negative) (77).

Evidence from several small, open trials suggested a positive effect of adjunctive aripiprazole in

patients with bipolar depression (78–83), but this has not yet been assessed in double-blind trials in patients with bipolar depression. However, adjunctive aripiprazole has been approved by the Food and Drug Administration (FDA) for the treatment of unipolar depression, and may be useful as add-on therapy in patients with bipolar depression as well.

Section 5. Maintenance therapy for bipolar disorder

Adherence

A Web-based survey among 469 patients with self-reported BD (n = 469) found that patients were more likely to be adherent if they were Caucasian and had more education, and if the medication reduced the severity of depressive episodes and did not cause weight gain or cognitive side effects (84). For example, 69% of Caucasian patients with at least a college degree were always or usually adherent, whereas only 34% of nonwhite patients with only eight years of education were always or usually adherent.

Predictors of recurrence

In the STEP-BD study, residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year predicted depressive recurrence, and residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year predicted manic, hypomanic, or mixed episode recurrence (85). In addition, prior history of rapid cycling was associated with a greater risk of further recurrences (86). Targeting residual symptoms in maintenance treatment may represent an opportunity to reduce risk of recurrence.

Similarly, data from long-term follow-up of patients in the National Institute of Mental Health Collaborative Depression Study, including 223 patients with BD I or BD II, found that patients with residual affective symptoms had a three times higher risk of recurrence compared to patients who achieved an asymptomatic state (87). History of three or more affective episodes before intake was also a significant predictor of recurrence. Therefore, the Committee recommends that acute episodes need to be treated aggressively until full remission to decrease the likelihood of relapse during the maintenance phase.

There is some evidence that switching medication after an acute response may predict poorer outcomes during maintenance therapy. In a post hoc analysis of a 12-month study, patients treated acutely with divalproex who continued on divalproex maintenance therapy had better outcomes than those who were switched to lithium or placebo (88).

Psychosocial interventions for maintenance therapy

A Cochrane database review of six RCTs found that interventions (self-help and psychosocial) that teach patients to recognize and manage early warning symptoms were beneficial in improving time to any, manic/hypomanic, and depressive recurrences, in reducing hospitalization rates, and in improving functioning (89).

A systematic review and meta-analysis of randomized or quasi-randomized controlled trials confirmed that CBT and group psychoeducation were beneficial as adjuncts to pharmacological maintenance treatments (90, 91). Family therapy was equivalent to individual psychosocial therapy and crisis management (90), but a Cochrane Database systematic review found no significant added effect for adjunctive family interventions compared to no intervention (92). One RCT demonstrated that a psychoeducational group intervention (12 sessions) focusing on caregivers only was effective in preventing any recurrence and hypomanic/manic recurrences in 113 euthymic patients with BD over a 12-month follow-up (93).

A six-month RCT in 52 stable patients with BD I or II confirmed the efficacy of cognitive therapy (CT) compared to treatment as usual as adjunct to lithium/divalproex (94). Adjunctive CT was associated with less severe depression scores, less dysfunctional attitudes, and longer time to depressive relapse. One-year follow-up showed a trend toward lower mania scores and improved behavioural self-control, which indicated some continuation of benefits. In addition, a pilot study in 14 remitted patients with BD found that mindfulness-based cognitive therapy had an immediate effect on between-episode residual anxiety and depressive symptoms among patients with suicidal ideation or behaviour compared to a wait-list condition (95).

The STEP-BD study found that intensive psychotherapies (FFT, IPSRT, and CBT weekly and biweekly for up to 30 sessions in nine months) were more effective than three sessions of individual psychoeducation (56). However, an 18-month, single-blind RCT in 204 patients with BD I or BD II found no significant clinical benefits with individual CBT (20 sessions) over group psychoeducation (six sessions) as adjunct to maintenance BD medications (lithium, divalproex, atypical an-

tipsychotics) (96). Both groups showed significant reduction in Longitudinal Interval Follow-up Evaluation scores for mania/hypomania and depression over time, with no significant differences between groups in reduction in symptom burden, recurrence rates, or completion rates (about 66%). However, psychoeducation cost $160 per patient compared to $1,200 per patient for CBT. The lower cost and potential ease of dissemination of group psychoeducation suggest that it may be beneficial to try this approach first, with additional psychosocial interventions reserved for those with continued symptoms. Additional data in favour of psychoeducation come from an RCT in which psychoeducational group intervention focusing on caregivers only was effective in preventing recurrence in euthymic patients with BD (93).

A one-year, single-blind RCT in 79 BD I or II patients compared seven sessions of individual psychoeducation to 20 sessions of CBT, with no differences in terms of relapses but modest differences in number of days with any depressed mood (97).

Pharmacological treatments for maintenance therapy

Most maintenance trials used an enriched study design, meaning that they randomized into the double-blind phase only those patients who showed a response to the test drug during the acute mood episode. Lithium is an exception, as some of the older lithium maintenance studies did not use this design and were still able to show superiority of lithium over placebo in preventing relapses. The implication of these data is that whatever treatment worked during the acute phase is likely to be effective in the maintenance phase. So, for example, if acute mania was effectively treated with lithium, divalproex or an atypical antipsychotic, the same medication should be continued for prevention of relapse [please see the original 2005 guidelines, Section 5: Maintenance therapy for bipolar disorder, General principles (1)].

Data from several new clinical trials in maintenance therapy for BD support several additions to the treatment recommendations (Table 5.5) (1, 2). There is now evidence for additional first-line options, including quetiapine monotherapy and adjunctive therapy for the prevention of manic and depressive events, aripiprazole monotherapy for the prevention of manic events, as well as risperidone long acting injection (LAI) monotherapy and adjunctive therapy and adjunctive ziprasidone for the prevention of mood events.

Table 5.5. Recommendations for maintenance pharmacotherapy of bipolar disorder

First line	Lithium, lamotrigine monotherapy (limited efficacy in preventing mania), divalproex, olanzapine, ***quetiapine***[a], ***lithium or divalproex + quetiapine***[a], ***risperidone LAI***[a], ***adjunctive risperidone LAI***[a], ***aripiprazole (mainly for preventing mania)***[a], ***adjunctive ziprasidone***[a]
Second line	Carbamazepine, lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third line	Adjunctive phenytoin, adjunctive clozapine, adjunctive ECT, adjunctive topiramate, adjunctive omega-3-fatty acids, adjunctive oxcarbazepine, or adjunctive gabapentin
Not recommended	Adjunctive flupenthixol, monotherapy with gabapentin, topiramate or antidepressants

LAI = long acting injection; ECT = electroconvulsive therapy.
[a]**New**.

First line: A meta-analysis of 14 RCTs (n = 2,526) confirmed the efficacy of lithium, lamotrigine, divalproex, and olanzapine for first-line use as maintenance therapy for bipolar disorder (98). Lithium [hazard ratio (HR) 0.68], lamotrigine (HR 0.68), divalproex (HR 0.82), and olanzapine (RR 0.58) were more effective than placebo in preventing relapse of any mood episode. Lithium and olanzapine significantly reduced manic relapses, while lamotrigine and divalproex significantly reduced depressive relapses. Lithium was more effective than lamotrigine, and olanzapine was more effective than lithium, in significantly reducing manic relapses. Withdrawal due to an adverse event was approximately twice as likely with lithium compared with divalproex and lamotrigine.

Quetiapine. Five new RCTs have demonstrated the efficacy of quetiapine alone or in combination with lithium/divalproex for maintenance therapy in bipolar disorder (64, 65, 99–103) (Level 1). In these studies, patients in remission after acute treatment were randomized to quetiapine or placebo maintenance therapy with the primary endpoint being recurrence of any mood event.

Two studies, EMBOLDEN I (64) and II (65), assessed quetiapine monotherapy in patients in remission after eight weeks of double-blind treatment. Pooled and individually, the EMBOLDEN studies demonstrated that the acute efficacy of quetiapine in bipolar depression was maintained in continuation treatment for 26–52 weeks compared with placebo (99). In a pooled analysis, recurrence

of a mood event was reported in 24.5% (71/290) of patients in the quetiapine group and 40.5% (119/294) of patients in the placebo group. The risk of recurrence of any mood event (HR 0.51, $p < 0.001$) or a depression event (HR 0.43, $p < 0.001$) was significantly lower with quetiapine than placebo. Time to recurrence of a mania/hypomania event did not reach significance (HR 0.75).

A recent 104-week RCT compared the efficacy of quetiapine, lithium, or placebo monotherapy in patients who were stable for at least four weeks following up to 24 weeks of quetiapine therapy. The study was stopped after a planned interim analysis (~56 weeks) revealed statistically significant benefits. Quetiapine was significantly more effective than placebo in reducing the risk of any mood event (HR 0.29), including both manic (HR 0.29) and depressive episodes (HR 0.30), or any episode $p < 0.001$ (100). Lithium was also more effective than placebo on all three measures. In addition, quetiapine was more effective than lithium for prevention of any event or depressive events, but the two therapies were similar for prevention of manic events.

Two RCTs have assessed the efficacy of adjunctive quetiapine maintenance therapy (101–103). Patients were randomized to lithium or divalproex plus quetiapine or placebo after achieving at least 12 weeks remission with open-label lithium or divalproex plus quetiapine (101–103). Pooled and individually, these studies demonstrated that quetiapine in combination with lithium or divalproex was significantly more effective than lithium or divalproex alone in the prevention of mood episodes during continuation treatment for up to 104 weeks (103).

Data from these two studies suggest that quetiapine, like other atypical antipsychotics such as olanzapine, can cause clinically meaningful increases in insulin resistance, which may lead to new or exacerbated cases of type 2 diabetes (101–103) (see safety section for more details). Further study is necessary to accurately estimate incidence and risk since these two studies were not designed to assess this concern.

Lithium. Additional long-term follow-up data confirm the utility of lithium for maintenance therapy. A two-year naturalistic follow-up study compared illness recurrence among patients who continued (n = 159) or discontinued (n = 54) lithium after an extended period of clinical stability on monotherapy (104). Continued lithium was associated with an almost fivefold lower risk of recurrence. The authors concluded that lithium discontinuation in BD after successful maintenance monotherapy is not advisable. A survey of 106 patients found that patients' knowledge levels regarding lithium treatment, including patients' attitudes, general opposition to prophylaxis, fear of side effects, denial of therapeutic effectiveness and illness severity, were directly correlated to treatment adherence (105).

Divalproex. There is good evidence to support the use of divalproex for maintenance therapy in BD. More recently, a prospective, open-label, crossover study found that when converting stable patients with BD from twice-daily divalproex delayed release to once-daily divalproex extended release, the total daily dose should be increased by 250–500 mg to ensure maintenance of therapeutic valproic acid levels (106).

Risperidone long-acting injection. Although the long-term efficacy of oral risperidone has not been assessed, two RCTs have examined the efficacy of risperidone LAI for maintenance treatment in BD (Level 1) (107, 108). In the first study, patients who were currently manic or stabilized on oral risperidone or other atypical antipsychotic received three weeks open-label treatment with oral risperidone, followed by 26 weeks open label treatment with risperidone LAI (107). Patients who remained stable were randomized to continue the same dose of risperidone LAI (n = 154) or switched to placebo injection (n = 143) for 24 months. Significantly fewer patients in the risperidone LAI group (29%) relapsed to any mood episode compared with those in the placebo group (57%).

The second study assessed risperidone LAI as an adjunct to treatment as usual in 139 patients who had frequently relapsing BD (requiring intervention for four or more episodes in the past year) (108). Patients who remained stable after 16 weeks of open-label adjunctive risperidone LAI were randomized to continued adjunctive risperidone LAI or switched to adjunctive placebo injection. Significantly fewer patients in the adjunctive risperidone LAI group relapsed (22%) to any mood episode compared with those in the placebo group (49%).

Since risperidone is the active moiety in the risperidone LAI, based on these data, risperidone oral and risperidone LAI are included as first-line treatments for maintenance treatment of BD.

Aripiprazole. Two RCTs have now demonstrated the efficacy of aripiprazole for maintenance treatment of patients with BD I (Level 1) (109–111).

A 26-week RCT reporting the efficacy of aripiprazole in the prevention of manic but not depressive relapses, previously cited in abstract form, has now been published (109). This study was designed a priori with a prospective, 74-week, double-blind,

placebo-controlled extension phase (110). At 100 weeks, as was seen in the 26-week results, aripiprazole continued to be superior to placebo in delaying time to manic relapse, but not depressive relapse.

A second study demonstrated the long-term efficacy of aripiprazole over 30 weeks of treatment in 296 pediatric patients with BD I (111). Aripiprazole 10 mg and 30 mg groups were significantly better than placebo in improving manic symptoms; response rates were 50%, 56% and 27%, respectively.

Given that efficacy was shown primarily for mania, aripiprazole is included as a first-line maintenance treatment for bipolar disorder for the treatment and prevention of mania.

Ziprasidone. The efficacy of adjunctive ziprasidone for maintenance treatment of bipolar mania was demonstrated in a six-month RCT in 239 patients with BD I who were stabilized for at least eight weeks on open-label therapy (Level 2) (112). The time to intervention for a mood episode was significantly longer with ziprasidone; 19.7% and 32.4% of patients in the ziprasidone and placebo groups, respectively, required intervention for a mood episode. Given that there is now clinical experience with ziprasidone, this agent can be recommended as a first-line option.

Third line:

Oxcarbazepine. A 52-week RCT in 55 patients with BD I and BD II found a lower risk of recurrence with oxcarbazepine (38%) compared to placebo (59%) as adjuncts to ongoing treatment with lithium, but this difference was not significant (Level 2, negative) (113). Lack of significant difference is likely to be due to lack of power due to smaller sample size in the study, as the differences in relapses were substantial between the two groups. There was also a trend toward fewer depressive episodes and better functionality with oxcarbazepine. Therefore, oxcarbazepine remains a third-line option.

Section 6. Special populations

Issues in the management of bipolar disorder in women

A secondary analysis of a large survey assessed the prevalence of, and association between, reproductive cycle-associated mood symptoms and affective disorders in women (114). Of 2,524 women with mood disorders, 67.7% reported premenstrual symptoms. Of those at risk, 20.9% reported postpartum symptoms and 26.4% reported perimenopausal symptoms. The rates did not differ between women with MDD and BD but were significantly different from women who were never ill. The occurrence of reproductive cycle-associated symptoms predicted the occurrence of MDD but not BD.

Pregnant women should be universally screened for BD by inquiring about personal and family history of BD. There is a need for valid screening instruments to detect hypomania/mania as well depression in pregnant or postpartum women with BD. The Mood Disorder Questionnaire has not been validated in pregnant women and the Edinburgh Depression Scale has not been studied in women with postpartum bipolar depression.

Management of acute episodes during pregnancy: Findings from case-control studies suggest no significant associations between overall maternal SSRI use during early pregnancy and risk of birth defects (115, 116). However, data suggest that individual SSRIs may confer increased risk for some specific defects, but these defects are rare and the absolute risks are small.

In utero exposure to SSRIs can also have an impact on the neonate, with reports of neonatal abstinence syndrome (117) and persistent pulmonary hypertension of the newborn (118). Data on the effect of atypical antipsychotics on birth weight are conflicting, with one study reporting significantly higher birth weights among infants exposed to atypical antipsychotics (119) and another reporting a trend toward lower birth weights (120).

Maintenance therapy during pregnancy: During a prospective, cohort study involving 89 pregnant women with BD, the overall risk of at least one recurrence in pregnancy was 71% (121). Among women who discontinued versus continued lithium/divalproex treatment, recurrence risk was twofold greater and the median time to first recurrence was more than fourfold shorter. Time to recurrence was 11-fold shorter with abrupt versus gradual discontinuation of lithium/divalproex. Most recurrences were depressive or mixed, and 47% occurred during the first trimester. Similarly, the risk of recurrence was substantially reduced when lamotrigine therapy was continued compared to discontinuation of lithium/divalproex therapies in a survey of 26 pregnant women with BD (122). The risk of new illness episodes was 30% with lamotrigine versus 100% after discontinuing lithium/divalproex, and time to recurrence was 12-fold longer.

Treatment planning for pregnant women with BD should consider not only the relative risks of fetal exposure to lithium/divalproex but also the high risk of recurrence and morbidity associated with stopping maintenance treatment.

The previous guidelines suggested that lamotrigine may be considered for maintenance therapy during pregnancy, particularly in patients who primarily suffer depressive relapses, as data from a large pregnancy registry suggested no increased teratogenicity (123). More recently, the FDA issued an alert stating that preliminary data from the North American Drug Pregnancy Registry suggested a possible link between lamotrigine exposure during the first trimester and the incidence of cleft lip/palate (124). However, they also stated that other pregnancy registries of similar size have not replicated this observation, and the clinical significance of this report is thus uncertain.

Management of bipolar disorder during the postpartum period: A Danish, population-based, cohort study found a 24-fold increase in the risk of postpartum mental disorders for women who have a first-degree relative with BD compared to a reference group (125). Family psychopathology represented a particular risk in the immediate postpartum period, especially if a family member suffers from BD compared to other diagnostic groups.

The diagnosis of BD is frequently missed in women with postpartum depression. Hypomania after childbirth may be misconstrued as the normal joy related to the experience of motherhood. In a survey of 56 women referred for postpartum depression, over half had a bipolar diathesis (126). The primary diagnoses were: MDD (46%), BD NOS (29%), BD II (23%), and BD I (2%).

In a retrospective survey of 127 women who developed a bipolar affective puerperal psychosis within four weeks of childbirth, there was a high prevalence of early-onset hypomanic symptoms (127). Onset of symptoms occurred within three days of delivery in 73% of women. The most common symptoms were: feeling excited, elated, or high; not needing or not being able to sleep; feeling active or energetic; and talking more or feeling very chatty. These types of symptoms should be carefully monitored in individuals at high risk of puerperal psychosis episodes.

Postpartum hypomania has been reported in 10-20% of women after childbirth (128–130). In addition, there was no phase in a woman's life, or for that matter a man's, when the point prevalence of hypomania reached the level in the postpartum period (131). The DSM-IV does not acknowledge hypomania as a postpartum-onset specifier, which means that women with BD II are likely often misdiagnosed as having MDD. The high prevalence of postpartum hypomania immediately after delivery highlights its importance as a window of opportunity to understand the biological underpinnings of BD.

Antidepressants should be used cautiously in women with postpartum depression due to the risk of induction of postpartum psychosis, mania, and rapid cycling. There are case reports of early-onset postpartum depression in which bipolarity manifested following antidepressant treatment (132). In each case there was no past history of psychiatric disturbance but there was a family history of BD.

Several authors have reported on the implications of psychotropic medications on breastfeeding (133–135). A systematic review of antidepressant and mood stabilizer use during lactation concluded that SSRIs, tricyclic antidepressants (except doxepin), carbamazepine, sodium valproate, and low doses of short-acting benzodiazepines were relatively safe for the breast-fed infant (133). However, if treatment with an SSRI is started in the postpartum period, fluoxetine and citalopram may not be drugs of first choice as case reports have described adverse effects in breast-fed infants. A case report on the use of oxcarbazepine during breastfeeding found that the concentrations of oxcarbazepine and its metabolite were acceptable (134). There are also emerging data about quetiapine during lactation. In a series of six women receiving quetiapine augmentation to antidepressants during lactation (135), no quetiapine was detected in breast milk in four of the six cases, and in all cases, estimated levels of infant quetiapine exposure were < 0.01 mg/kg/day. Four of the six babies showed typical development and two showed slight developmental delays. Levels of quetiapine were not detectable in breast milk in the mothers of the two infants showing mild delays.

The American College of Obstetricians and Gynecologists (ACOG) clinical management guidelines categorized the lactation risk of psychiatric medications using the following criteria: L1 = safest; L2 = safer; L3 = moderately safe; L4 = possibly hazardous; L5 = contraindicated. The most common bipolar medications were categorized as follows: lithium (L4), divalproex (L2), carbamazepine (L2), lamotrigine (L3), olanzapine (L2), risperidone, aripiprazole, and clozapine (L3), and quetiapine and ziprasidone (L4) (136).

Issues in the management of bipolar disorder in children and adolescents

As in previous guidelines, treatment recommendations for pediatric bipolar disorder are beyond the scope of these guidelines; the reader is referred to specific guidelines for management of children and adolescents developed by the American Academy of Child and Adolescent Psychiatry (137). Therefore, in the following section, we will provide only a brief overview of some of the issues in this population.

Presentation and diagnosis: After first hospitalization for BD, over half of adolescent patients experienced a recurrence, and only 35% were fully adherent to medication (138). Predictors of poor recovery included comorbid attention-deficit hyperactivity disorder (ADHD), anxiety disorders, disruptive behaviour disorders, alcohol use disorders, and treatment with antidepressants, as well as nonadherence to psychotropic medication, lower socioeconomic levels, and female gender. A meta-analysis of five open trials also showed that comorbid ADHD was associated with a reduced response to pharmacotherapy in the treatment of acute mania (139).

A recent analysis demonstrated the reliability of the Young Mania Rating Scale (YMRS), Kiddie Schedule for Affective Disorders Mania Rating Scale, and the Children's Depression Rating Scale–Revised for the differential diagnosis of BD across a broad age range (4–17 years) (140). Psychotic symptoms, particularly delusions of grandiosity, are common in children with BD I, being present in 76% of patients (141).

Acute and maintenance treatment of pediatric bipolar disorder

Psychosocial interventions. A small, open trial in 34 pediatric patients with BD found that a maintenance model of child- and family-focused CBT was associated with positive effects on symptoms and functioning over a three-year follow-up period (142).

Small pilot studies have demonstrated that multifamily psychoeducation groups and individual family psychoeducation were beneficial in the treatment of pediatric patients with BD (143). There were improvements in mood and family climate and possible improvements in treatment utilization at end of treatment and at six-month follow-up.

Pharmacological management. The strength of evidence for efficacy of various treatments in pediatric bipolar disorder is outlined in Table 6.8.

Lithium and divalproex: As reported previously, there are Level 2 RCT data to support the use of lithium and divalproex for the treatment of pediatric patients with BD (1, 2).

Atypical antipsychotics: The efficacy of olanzapine in the treatment of adolescent mania that was previously cited in abstract form has now been published (Level 2) (144). Olanzapine was associated with significantly higher response and remission rates compared to placebo. However, patients treated with olanzapine had significantly greater weight gain and increases in hepatic enzymes, prolactin, fasting glucose, fasting total cholesterol, and uric acid, which may be a concern in adolescents in need of lifelong treatment.

The efficacy of quetiapine has previously been demonstrated in children and adolescents with BD as both monotherapy (Level 2) (145) and adjunctive therapy (Level 2) (20). Recent data showed that quetiapine and divalproex were equally effective in improving impulsivity and reactive aggression in a four-week RCT involving 33 adolescents with BD and comorbid disruptive behaviour disorders (146).

A large four-week RCT demonstrated the efficacy of ziprasidone monotherapy in improving mania symptoms in 238 children and adolescents with BD (Level 2) (147). Therapy was well tolerated, with no changes in lipid or glucose levels. In addition, ziprasidone was efficacious in a small, eight-week, open-label trial (148).

An RCT with a four-week acute phase and a 26-week continuation phase demonstrated the acute and long-term efficacy of aripiprazole in 296

Table 6.8. Strength of evidence for treatments for pediatric bipolar disorder

Agent	Level of evidence
Lithium	2
Anticonvulsants	
Divalproex	2
Oxcarbazepine	2 (–ve)
Atypical antipsychotics	
Olanzapine	2
Quetiapine	2
Ziprasidone	2
Risperidone	2*
Aripiprazole	2
Combination therapy	
Adjunctive lithium	4
Adjunctive lamotrigine	3 (depression)
Olanzapine or risperidone + lithium or divalproex	3/4
Quetiapine + divalproex	2
Electroconvulsive therapy	3

*Approved by the FDA for use in pediatric bipolar disorder for children aged 10 and above, but the trial supporting the evidence has not been presented at conferences.

pediatric patients with BD I (Level 2) (111, 149). Aripiprazole 10 mg and 30 mg groups were significantly better than placebo in improving manic symptoms; response rates at week 4 were 45%, 64%, and 26%, and at week 30 were 50%, 56% and 27%, respectively. In addition, aripiprazole monotherapy was associated with significant improvements in YMRS scores versus baseline in a small, eight-week, open-label trial (150).There was no statistically significant increase in body weight, but aripiprazole was associated with two dropouts due to extrapyramidal symptoms. Aripiprazole was effective in a six-week open trial in 10 pediatric patients with BD and comorbid ADHD, significantly improving both manic and ADHD symptoms (151).

Other treatments: A seven-week RCT found no significant improvement in mania symptoms with oxcarbazepine in 116 youths with BD I manic or mixed episode, compared to placebo (Level 2, negative) (49). In an eight-week open trial in 20 pediatric patients with BD I, omega-3 fatty acids, combined eicosapentaenoic acid and docosahexaenoic acid, were associated with modest improvement, with only 35% of patients showing response (152). Methylphenidate was effective for the management of ongoing ADHD symptoms in euthymic pediatric patients with BD (153).

Issues in the management of bipolar disorder in older patients

Presentation and course: Additional data provide further evidence that age minimally influences manic psychopathology but not overall severity in patients with BD (154).

Several studies have demonstrated cognitive impairment in older patients with BD, which are similar to those reported in younger patients (155–159). Compared to age-matched controls, older patients with BD had more extrapyramidal symptoms and worse performance in psychomotor speed, selective attention, verbal memory, verbal fluency, and executive functions, as well as poorer psychosocial functioning (155–159). Neurocognitive deficits can contribute to medication errors and nonadherence to treatment (160). Older patients with BD made almost three times as many medication errors compared to normal control subjects. Within the BD group, there was a significant correlation between medication errors and dementia scores, particularly memory, but not with age, education, depression scores, number of psychiatric medications, or medical conditions.

Comorbidity: The overall burden of comorbid medical conditions was comparable in elderly patients with BD and those with MDD, but patients with BD had higher body mass index (BMI) and greater burden of endocrine/metabolic and respiratory disease (161).

A large survey of geriatric patients with BD in a Veterans Health Administration database found that 29% of patients with BD had comorbid substance use disorder (8.9%), posttraumatic stress disorder (5.4%), other anxiety disorders (9.7%), or dementia (4.5%) (162). Patients with comorbid substance abuse were more likely to be younger, minority, unmarried, and homeless compared to patients with comorbid anxiety disorders or dementia. In a community survey, the lifetime rates of comorbid alcohol use disorders (38.1%), dysthymia (15.5%), generalized anxiety disorder (20.5%), and panic disorder (19.0%) were significantly higher among elderly respondents with BD compared to those without BD (163). However, elderly patients with BD had lower rates of alcohol use disorders, dysthymia, and panic disorder than younger patients.

Acute treatment of mania in older patients: Few data are available assessing BD pharmacotherapy in older patients (1, 2). A 12-week open trial of aripiprazole in 20 older patients with BD found significant reductions in depression (HAM-D) and mania (YMRS) scores, and significant improvement in functional status (164).

There is also preliminary evidence from two small, open studies to suggest that adjunctive levetiracetam may have beneficial antimanic effects in hospitalized geriatric patients with BD or dementia (165, 166). A small open study in 12 elderly patients with BD I or BD II with evidence of mild cognitive decrements found that treatment with donepezil had no significant effects on cognitive and functional measures (167).

Acute treatment of bipolar depression in older patients: In an open study involving 122 elderly unipolar or BD depressed outpatients, treatment in a psychiatric day hospital program that combined individual and group psychotherapy resulted in a significant reduction of depressive symptoms and improvement in quality of life (168).

Findings from a retrospective cohort study in older patients with BD suggest that those who received an antidepressant had a significantly lower likelihood of admissions for manic/mixed but not depressive episodes (169). As in younger patients, antidepressants should be used with caution in older patients with BD, since an increased risk of manic switch has been reported (2).

Maintenance treatment: Evidence from a retrospective chart review of 60 older patients with unipolar depression or BD showed that long-term lithium therapy was associated with improvements in frequency, severity, and duration of depressive or manic relapses, rate and duration of hospitalizations, and suicidal behaviour (170).

A pilot study of a 12-week manualized group intervention in 21 older patients with BD showed evidence of improved medication adherence, medication management ability, depressive symptoms, and some measures of health-related quality of life (171).

Issues in the management of bipolar disorder in patients with comorbid conditions

Epidemiology: Patients with BD have high rates of comorbid psychiatric (e.g., anxiety disorders, substance use disorders) and medical conditions (e.g., overweight/obesity, type 2 diabetes, cardiovascular disease, migraine, hepatitis C, HIV, dementia, lower back pain, chronic obstructive pulmonary disease, asthma, allergies) compared to the general population (1, 2).

A 20-year follow-up of the Zurich cohort (n = 591) showed that individuals with manic symptoms were at significantly greater risk for alcohol abuse/dependence, cannabis use and abuse/dependence, and benzodiazepine use and abuse/dependence (172). BD II predicted both alcohol abuse/dependence and benzodiazepine use and abuse/dependence. Substance abuse was a significant risk factor for criminal arrest in patients with BD, especially among women with BD (173). Comorbid substance abuse has also been associated with significantly poorer outcomes and lower rates of adherence to lithium/divalproex treatments (174, 175).

In the Canadian Community Health Survey (n = 36,984), rates of medical comorbidities, including chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, hypertension, and gastric ulcer were significantly higher in patients with BD compared to those without (176). Chronic medical disorders were also associated with a more severe course of BD, increased household and work maladjustment, receipt of disability payments, reduced employment, and more frequent medical service utilization. In addition, an elevated cancer risk in patients with BD has been reported in both men and women (177). Fibromyalgia has also been highly associated with BD, suggesting these conditions may share underlying pathophysiological links (178).

As reported previously (1, 2) and in Section 8, rates of metabolic syndrome and diabetes are elevated in patients with BD. In patients with BD, comorbid diabetes almost doubled the overall health care costs compared to patients without diabetes (179). Patients with psychiatric disorders and comorbid diabetes reported greater impairment in both physical and mental health, lower quality of life, and less satisfaction with health compared to those without diabetes (180).

Treatment of bipolar disorder in patients with comorbidities: The addition of either olanzapine or lamotrigine to lithium therapy in patients with remitted BD and a current anxiety disorder (n = 47) were effective in reducing Hamilton Anxiety Scale scores and Clinical Global Impressions (CGI)–Severity scores in a 12-week, randomized, single-blind study (181). This is limited evidence that adding a second agent (olanzapine or lamotrigine) to lithium is effective in reducing anxiety symptoms in patients with BD and a comorbid anxiety disorder.

In an eight-week RCT, risperidone monotherapy was not more effective than placebo in improving anxiety symptoms in patients with BD and comorbid panic disorder or generalized anxiety disorder (182).

Section 7. Bipolar II disorder: acute and maintenance management

Epidemiology

The National Comorbidity Survey Replication (n = 9,282) reported a lifetime prevalence of BD II of 1.1% (12-month prevalence 0.8%) (3). Other epidemiological studies have reported a lifetime community prevalence of about 5%, and that 50% of depressed outpatients have BD II (183). Mean age of onset was 20.3 years (3). Most respondents had lifetime comorbidity with other Axis I disorders, particularly anxiety disorders. Clinical severity and role impairment were greater for BD II than for BD I episodes of major depression. Only a minority of subjects with BD II in the community received appropriate medication (defined as lithium/divalproex, anticonvulsants, or antipsychotics).

A one-year naturalistic follow-up of patients with BD I (n = 405) and with BD II (n = 102) confirmed that patients with BD II are symptomatic approximately 50% of the time, and suggested that patients with BD I and BD II had the same tendency toward mood instability (184).

In the 20-year follow-up of the Zurich cohort (n = 591), the presence of BD II predicted the later development of alcohol abuse [odds ratio (OR) 9.1], alcohol dependence (OR 21.1), and benzodiazepine abuse/dependence (OR 14.1), but not cannabis use or abuse compared to subjects without BD II (172). In contrast, MDD was predictive only of later benzodiazepine abuse/dependence. The different risks of substance use emphasize the need to differentiate patients with BD II from those with MDD.

There is also evidence of functional and neurocognitive impairment. BD II is associated with long-term disability (185), with patients missing over a year of work in their lifetime due to psychiatric illness (186). Patients with BD II reportedly have a poorer health-related quality of life compared to those with BD I (187). Cognitive impairments including deficits in working memory, semantic fluency, attention, verbal memory, and executive functions have been demonstrated in patients with BD II compared to healthy controls (188, 189).

Diagnosis of bipolar II disorder

The ISBD Diagnostic Guidelines Task Force suggested revisions to both ICD-10 and DSM-V criteria for BD II and hypomania (4). The most significant suggestions involve the criteria for hypomania, changing the duration of symptoms from at least four days to at least two days, including the presence of mixed hypomania (hypomanic with depressive symptoms), and including hypomanic episodes potentially triggered by antidepressants and other substances (4, 190). The ISBD also suggested changes to the criteria for BD II; the exclusion of a mixed episode should be clarified as a mixed manic episode, and the requirement for symptoms to cause clinically significant distress or impairment should apply to depressive symptoms, since hypomanic symptoms may not be impairing. Please refer to the ISBD Diagnostic Guidelines Task Force Report for more information (4).

The biological validity of BD II was supported in a genetic study of 58 multiplex bipolar families which found evidence for linkage derived from BD II sibling pairs sharing marker alleles on chromosome 18q (191). Further analysis of 74 bipolar pedigrees found that BD II was associated with genetic heterogeneity. While there are some overall genetic findings in BD (e.g., chromosome 18q21), there may be distinct genetic markers for BD II (e.g., chromosome 9p13). However, neurobiological studies, involving magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, have not found conclusive differences between these groups thus far (192). This may be due to the small number of comparative studies available and perhaps to insufficiently powered samples, but if accurate, this suggests that BD I and BD II would respond comparably to similar treatments. Further research in this area would be highly useful.

Acute management of bipolar II depression

The majority of patients with BD II depression are inadequately treated. The National Comorbidity Survey Replication (n = 9,282) reported that only about 16% of patients with BD II received appropriate medication (defined as lithium/divalproex, anticonvulsants, or antipsychotics), while 60% received no medication (3). Similarly, data from the Jorvi Bipolar Study (193) found that only 44% of subjects with BD II were treated with lithium or an anticonvulsant (193). Patients with BD II were significantly more likely to receive treatment with an antidepressant compared to subjects with BD I. Only 31% of patients with BD II were considered to be receiving adequate pharmacotherapy. In a community sample of newly diagnosed patients with BD II (n = 1,001), 55% were prescribed an antidepressant (65% as monotherapy), compared to 31% who were prescribed lithium, an anticonvulsant, or an antipsychotic (194).

Tables 7.1 and 7.2 illustrate the strength of evidence and recommendations for pharmacological treatment of acute BD II depression.

Atypical antipsychotics. There are now four large RCTs demonstrating the efficacy of quetiapine monotherapy in combined groups of patients with BD I or BD II depression: BOLDER I (62) and II (63), which were cited in previous iterations of these guidelines; and two additional eight-week RCTs, EMBOLDEN I (64) and II (65), which have now been reported in abstract form. These four trials included substantial numbers of patients with BD II depression: BOLDER I (n = 181) and II (n = 170), EMBOLDEN I (n = 303) and II (n = 262). In patients with BD II depression in BOLDER I and EMBOLDEN I, improvements in MADRS were numerically but not statistically significant at endpoint (week 8), although they were significant at various weekly visits. In contrast, the BOLDER II and EMBOLDEN II trials showed significant benefits in the patients with BD II (Level 1). In addition, a post hoc pooled analysis of the patients with BD II depression from both BOLDER trials (n = 351) found that both doses

Table 7.1. Strength of evidence for monotherapy treatments of acute bipolar II depression

Agent	Level of evidence
Lithium	3
Anticonvulsants	
Divalproex	3
Lamotrigine	3
Gabapentin	3 (–ve)
Atypical antipsychotics	
Olanzapine	No data
Risperidone	No data
Quetiapine	1
Ziprasidone	3
Aripiprazole	No data
Clozapine	No data
Antidepressants	
Antidepressant monotherapy	4
Fluoxetine	3
Venlafaxine	3
Tranylcypromine	2
Combination therapy	
Lithium or divalproex + pramipexole	2
Lithium or divalproex + SSRI or bupropion	2 (–ve)
Lithium or divalproex + topiramate	3
Atypical antipsychotic + antidepressant	4
Lamotrigine + bupropion	2 (–ve)

SSRI = selective serotonin reuptake inhibitor.

Table 7.2. Recommendations for pharmacological treatment of acute bipolar II depression

First line	***Quetiapine***[a]
Second line	Lithium, lamotrigine, ***divalproex***[a], lithium or divalproex + antidepressants, lithium + divalproex, atypical antipsychotics + antidepressants
Third line	Antidepressant monotherapy (particularly for those with infrequent hypomanias), switch to alternate antidepressant, ***ziprasidone***[a]
Not recommended	See text on antidepressants for recommendations regarding antidepressant monotherapy

[a]**New**.

of quetiapine demonstrated significant benefits as early as week 1, which were sustained throughout the eight weeks (195). Two subanalyses of the BOLDER I data showed that among patients with BD II depression, quetiapine was effective in patients with rapid cycling (196), but anxiety scores (HAM-A) were not significantly improved (197). However, in the pooled analysis of BOLDER I and II, the changes in HAM-D, HAM-A, and CGI were significantly greater for both quetiapine groups versus placebo, and quetiapine 600 mg/day was effective in both rapid and non-rapid cycling depression (195). Based on statistically significant improvements in two RCTs and numerically superior improvements in two additional trials, quetiapine monotherapy can now be recommended as a first-line treatment.

An eight-week open trial of ziprasidone in 20 patients with BD II depression found significant improvements in depression scores within 1–2 weeks, which were sustained to end of treatment (Level 3) (198).

Lithium and anticonvulsants. In addition to previous data noted in the 2005 guidelines (1), evidence from several open studies supports the effectiveness of lithium, lamotrigine, and divalproex in the acute treatment of patients with BD II depression. A 16-week, open, randomized trial assessed the efficacy of lithium (n = 56) or lamotrigine (n = 46) monotherapy in patients with acute BD II depression (Level 3) (199). Mean MADRS scores significantly decreased from baseline in both groups (lamotrigine from 28.9 to 12.5 and lithium from 29.9 to 15.2), with no differences between the two treatments. There were no differences in response between patients with rapid cycling (72% of patients) or without, although there was a high dropout rate in the rapid cycling group (42% of patients).

Divalproex ER, mainly used as monotherapy but also as augmentation, was effective in a seven-week, open trial in 28 patients with BD II depression (Level 3) (200). Response was statistically similar with monotherapy (45%, n = 21) and adjunctive therapy (71%, n = 7).

Antidepressants. The risk-benefit ratio for antidepressant use in BD II is still an unresolved issue. The STEP-BD study, comparing adjunctive antidepressants (bupropion or paroxetine) plus lithium or divalproex and lithium or divalproex alone, for up to 26 weeks, included 114 patients with BD II (67). In the combined sample (BD I and BD II) as well as between BD I and BD II patients, rates of durable recovery (eight consecutive weeks of euthymia) were comparable for adjunctive antidepressants and lithium or divalproex alone (Level 2, negative). This study, with its practical and clinically meaningful outcome, does not definitively establish that antidepressants are useless in bipolar depression, but it does compel careful thought about the use of antidepressants in depression.

In a small, nine-month, randomized, crossover trial involving 10 treatment-naïve patients with BD II, SSRI treatment led to a significant reduction in depression severity, percentage of days depressed or high, and percentage of days impaired, without illness destabilization, when compared with placebo (Level 4) (201). In addition, a post hoc analysis of a placebo-controlled RCT of antidepressant monotherapy in 248 unipolar and 62 BD II patients found that both groups benefited

comparably from active treatment, with no switch noted in the BD II patients (Level 4) (202).

Venlafaxine and bupropion have also been evaluated. A 12-week, open, randomized trial in 83 patients with BD II depression found that there were higher response and remission rates with venlafaxine compared to lithium (Level 3) (203). Discontinuation rates were significantly lower with venlafaxine compared to lithium, and there was no evidence of hypomanic switch in either group. On the other hand, a 16-week RCT of adjunctive bupropion in 20 patients with BD II depression who had an inadequate response to eight weeks of lamotrigine found no differences between bupropion and placebo on either depression or mania scores (Level 2, negative) (204).

Whether the risk of hypomanic switch or cycle acceleration with antidepressants in patients with BD II is less than in those with BD I remains controversial (1). Among patients treated with adjunctive antidepressants in a 10-week trial, those with BD II had significantly fewer switches (2%) than subjects with BD I (12%) (205). Further, a recent systematic review also reported that switch rates with antidepressants are lower in patients with BD II compared with those with BD I (206).

Maintenance therapy for bipolar II disorder

The focus of long-term therapy for patients with BD II is prevention of depressive episodes. Recommendations for maintenance treatment remain unchanged from the 2005 and 2007 guidelines, with lithium and lamotrigine continuing to be the recommended first-line agents (Tables 7.3 and 7.4)

Table 7.3. Strength of evidence for maintenance treatments of bipolar II disorder

Agent	Level of evidence
Lithium	2
Anticonvulsants	
Divalproex	3
Lamotrigine	2
Carbamazepine	3
Gabapentin	4
Atypical antipsychotics	
Adjunctive risperidone	3
Antidepressants	
Fluoxetine	3
Imipramine	2 (–ve)
Combination therapy	
Lithium + imipramine	2 (–ve)
Lithium + SSRI, venlafaxine or bupropion	4
Electroconvulsive therapy	4

SSRI = selective serotonin reuptake inhibitor.

Table 7.4. Recommendations for maintenance treatment of bipolar II disorder

First line	Lithium, lamotrigine
Second line	Divalproex, lithium or divalproex or atypical antipsychotic + antidepressant, combination of two of: lithium, lamotrigine, divalproex, or atypical antipsychotic
Third line	Carbamazepine, atypical antipsychotic, ECT
Not recommended	Gabapentin

ECT = electroconvulsive therapy.

(1, 2). Although quetiapine is recommended as a first-line option for the acute treatment of BD II depression, long-term data are not yet available. The pooled analyses from EMBOLDEN I and EMBOLDEN II trials for maintenance treatment of BD II depression are awaited.

Lamotrigine. Two retrospective, naturalistic studies including a total of 61 patients with BD II reported clinical improvements with lamotrigine, primarily used in combination with antidepressants or lithium/divalproex, for an average of 20 months (207, 208). These data provide additional support for the use of adjunctive lamotrigine in patients with BD II.

Bipolar spectrum disorders

Patients with bipolar spectrum disorders are commonly seen in clinical practice, and many of these patients have significant alterations in function and require treatment. Yet virtually no double-blind, controlled trials assessed the efficacy of treatments for patients with these disorders. In the absence of evidence, definitive treatment recommendations cannot be made and clinicians are advised to treat these patients on a case-by-case basis using their clinical experience and evidence from open-label studies. Given the prevalence of these disorders in clinical practice, studies are urgently needed to assess the efficacy of treatments for patients with bipolar spectrum disorders.

Section 8. Safety and monitoring

Monitoring

The 2005 and 2007 CANMAT guidelines for the management of BD provided recommendations for initial and follow-up laboratory investigations and monitoring for patients with BD (1, 2). Evidence continues to accumulate that patients with BD are at increased risk of comorbid medical conditions, which may be further increased by some of the treatments for BD. Several

Table 8.1. Baseline laboratory investigations in patients with bipolar disorder

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

TC = total cholesterol; vLDL = very low-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglyceride; eGFR = estimated glomerular filtration rate.

risk factors for cardiovascular disease are elevated in patients with BD, particularly with atypical antipsychotic treatment; these include overweight/obesity, diabetes, metabolic syndrome, and dyslipidemia.

Ideally, complete medical and baseline laboratory investigations should be performed before initiation of pharmacological treatment for BD as outlined in Table 8.1. However, if an acute clinical situation precludes immediate evaluation, assessments should be performed as soon as possible. Patients with BD should be regularly monitored for weight changes and adverse effects of medication.

Clinical practice in terms of monitoring could be improved (209, 210). In one two-year survey of patients with BD, only 40% received a serum drug level for lithium/divalproex, and 39% received a thyroid function test for lithium (209). Over 70% of patients received complete blood counts and hepatic function tests for valproate or carbamazepine, but of those prescribed atypical antipsychotics, only 50% received cholesterol counts and 69% received serum glucose levels. In another survey, 78% of psychiatrists reported monitoring weight, 69% glucose, 61% lipids, and 52% blood pressure (210).

Safety and tolerability of pharmacotherapy for bipolar disorder

The 2005 and 2007 CANMAT guidelines for the management of bipolar disorder extensively reviewed the safety and tolerability of pharmacotherapeutic options; only new data are included here (1, 2).

Systematic reviews and meta-analyses of pharmacotherapy RCTs for BD have confirmed the most common side effects of the various treatments (13, 14, 16, 25, 37, 44, 98). During acute therapy, carbamazepine, aripiprazole, and lithium had higher withdrawal rates than placebo, while risperidone and aripiprazole were associated with higher rates of extrapyramidal symptoms (EPS) (13). During maintenance therapy, withdrawal due to adverse events was twice as likely with lithium compared to divalproex or lamotrigine (98). An analysis of 24 studies found that compared to placebo, the incidence of EPS was significantly higher with aripiprazole and risperidone, and numerically but not significantly increased with ziprasidone (14). In addition, weight gain was significantly greater with olanzapine and quetiapine but not with the other atypical antipsychotics, and all agents exhibited significantly higher rates of somnolence.

The most common adverse events with quetiapine were somnolence and dry mouth in a review of five RCTs (25). Quetiapine did not induce EPS, but weight gain was notable. A systematic review of six RCTs found that risperidone caused more weight gain, EPS, sedation, and increase in prolactin level compared to placebo, and more weight gain but less EPS than haloperidol (16). A systematic review of 15 trials found that haloperidol was associated with less weight gain than olanzapine, but a higher incidence of tremor and other movement disorders (44). As expected, combination therapy with lithium/divalproex plus an antipsychotic was associated with decreased tolerability and greater weight gain compared to lithium/divalproex monotherapy (37).

Weight gain: A naturalistic study found a 10% increase in the prevalence of obesity (from 25% to 35%) over just four weeks during in hospital treatment of acute mania (211). Largest weight increases were seen with olanzapine plus divalproex; patients on any atypical antipsychotic showed greater weight gain than those on typical antipsychotics or no antipsychotic.

A systematic review of 19 studies in 684 pediatric patients found that significant treatment-associated weight increases are common in children as well (212). Weight gain was greater with combined atypical antipsychotic plus lithium/divalproex (5.5 kg) compared to lithium/divalproex alone (1.2 kg) but not compared to antipsychotic monotherapy (3.4 kg).

Weight control interventions can be effective. A prospective, open study in 110 patients taking atypical antipsychotics found that an 18-month weight-control program significantly decreased body weight, BMI, and waist circumference, while

these parameters significantly increased in a control group (213). In addition, lipid profiles improved in the active group and worsened in the control group. An eight-week study found that treatment with olanzapine plus diet modifications and moderate physical activity was associated with a significantly smaller weight gain compared to treatment with olanzapine alone (2 kg versus 3.5 kg) (214). There is also evidence to suggest that patients with severe mental illness on long-term pharmacologic treatment have reduced basal energy expenditure and thus may be a cause of weight gain (215).

Metabolic syndrome and type 2 diabetes: There have been additional studies since the 2007 update to support previous reports of high rates of metabolic syndrome in patients with BD (216–218). In one analysis, 18-30% of consecutive patients met criteria for metabolic syndrome, and 7% had diabetes mellitus (216). Rates of metabolic syndrome were significantly higher in psychiatric patients receiving antipsychotics (27%) compared to those not receiving antipsychotics (14%) (217). In a systematic review, rates of metabolic syndrome in patients with BD were 25-50% (218).

Data from two maintenance studies suggest that adjunctive quetiapine (like other atypical antipsychotics) can cause clinically significant increases in insulin resistance, which may lead to new or exacerbated cases of type 2 diabetes (101–103). The incidence of adverse events potentially associated with type 2 diabetes was 3.1% in the quetiapine group compared with 1.0% in the placebo group. The estimated increased risk of type 2 diabetes with adjunctive quetiapine compared to placebo was about 6%, based on a single fasting blood glucose (FBG) > 126 mg/dL (7.0 mmol/L), and about 2.5% if a single FBG > 200 mg/dL (11.1 mmol/L) was the threshold. However, since these studies were not designed to assess this concern, further study is necessary to accurately estimate the risk of diabetes.

While data suggest an increased risk of type 2 diabetes with antipsychotic therapy (1, 2), the relative risks with individual agents remain poorly defined. A review of 25 observational studies found that the attributable risk of developing diabetes mellitus for individual atypical antipsychotics relative to conventional antipsychotics ranged from 53 more to 46 fewer new cases of diabetes per 1,000 patients, with little difference between the individual atypical antipsychotics (219). However, few of the studies controlled for body weight, race, or ethnicity, or the presence of diabetes medications, and none adjusted for familial history of diabetes, levels of physical activity, or diet.

Dyslipidemia: Additional epidemiologic studies provide further evidence of the risk of dyslipidemia with antipsychotic therapy (220, 221). A cross-sectional study found that glucose, very low-density lipoprotein, and triglyceride levels were higher, while high-density lipoprotein levels were lower, in patients with BD treated with atypical antipsychotics or lithium/divalproex than in controls (220). In another cohort study including 13,133 cases of hyperlipidemia and 72,140 matched control subjects, clozapine (OR 1.82), risperidone (OR 1.53), quetiapine (OR 1.52), olanzapine (OR 1.56), ziprasidone (OR 1.40), and conventional antipsychotics (OR 1.26), but not aripiprazole (OR 1.19), were associated with significantly increased risks of hyperlipidemia as compared with no antipsychotic medication (221).

Neurological side effects: In a meta-analysis of 11 RCTs, haloperidol significantly increased the risk for akathisia, overall EPS, and anticholinergic use (222). Among atypical antipsychotics, ziprasidone and risperidone significantly increased the risk for overall EPS and anticholinergic use, aripiprazole increased the risk of akathisia, and quetiapine increased the risk of overall EPS.

Dermatological reactions: Lamotrigine is associated with a risk of serious rash, including toxic epidermal necrolysis and SJS (1). A case control study reported that the risk of severe skin reactions was increased 14-fold by use of lamotrigine (223). The risk may be increased by concomitant administration of divalproex (1) or aripiprazole (224).

Carbamazepine has also been associated with an increased risk of rash and SJS (1). Recently, the FDA recommended a boxed warning be added to carbamazepine preparations stating that dangerous or even fatal skin reactions (SJS and toxic epidermal necrolysis) can occur, and are significantly more common in patients with human leukocyte antigen allele HLA-B*1502, primarily found in patients of Asian ancestry (225).

High rates of serious dermatological reactions including erythema multiforme and SJS have been reported in children taking modafinil, probably because of the much higher doses on mg/kg basis in these individuals (71). Modafinil should be used with caution in patients with low body weight.

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