2013 VOLUME 2, ISSUE 1

Mood and Anxiety Disorders Rounds™

A PHYSICIAN LEARNING RESOURCE FROM THE CANADIAN NETWORK FOR MOOD AND ANXIETY TREATMENTS

CANMAT 2013 Update of Guidelines for the Management of Patients with Bipolar Disorder

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Bipolar disorder (BD) is among the most challenging conditions for clinicians to treat, a challenge that CANMAT has attempted to address through publication of treatment guidelines for BD in 1997, 2005, 2007, 2009, and now with a 2013 update. As fully described in the original guidelines, classic methodology was used in creating them, including rating of evidence based on standardized criteria, coupled with clinical recommendations incorporating the evidence ratings together with clinical consensus on the feasibility of the recommendation based on tolerability and safety. The full article has 8 sections covering all phases of BD and additional key topics. This issue of *Mood and Anxiety Disorders Rounds* outlines the most important elements included in the 2013 update, with an emphasis on what has changed; more comprehensive and detailed facts are found in the 2005 major article as well as the 2013 update, both published in the journal *Bipolar Disorders*.

Introduction – New Data on Epidemiology and Clinical Features

Bipolar disorder (BD), including a spectrum of subtypes, has been reported to affect up to 4% of the general population.[1,2] A study of 61 392 individuals across 3 continents largely confirms earlier findings, with lifetime rates of 0.6% for bipolar I disorder (BD-I),[a] 0.4% for BD-II,[a] and subthreshold BD at 1.4%.[3] Schaffer et al[4] calculated a 2.2% weighted lifetime prevalence rate among Canadians, with reduced prevalence and treatment rates in immigrant populations. Bulloch et al[5] estimated that 0.4%–1.2% of the Canadian population was being treated by psychiatrists for BD-I. Overall, these findings suggest that there has been significant progress in the diagnosis and treatment of BD in Canada.

Significant demographic and clinical characteristics associated with a diagnosis of BD included younger age, low income, diagnosis of an anxiety disorder, and substance abuse in the previous 12 months. The mean age of onset among Canadian BD patients was 22.5 years,[4] and the mean age at first manic/hypomanic or major depressive episode was reported to be as young as 18.2 years for BD-I in the United States National Comorbidity Survey Replication (NCS-R).[1] Perlis et al[6] found that 65.3% of subjects (N=983) enrolled in the National Institute of Mental Health's Systematic Treatment Enhancement Program for Bipolar Disorder experienced BD onset before age 19 and 27.7% before age 13. Kroon et al[7] identified 2 peaks in age at onset: 15–24 years and 45–54 years. A parental history of major depression, BD, or schizophrenia may reduce the age of first episode by 4–5 years compared with individuals with no such family history.[8]

There is a very high rate of concomitant medical and psychiatric conditions among BD patients.[9] Metabolic problems and anxiety disorders are among the most common, and require additional treatment strategies that have been highlighted in a series of Task Force Reports from the Canadian Network for Mood and Anxiety Treatments (CANMAT).[10-12]

BD is typically a lifelong disorder, characterized by a cycle of remissions and relapses. It significantly impairs a host of functional domains such as daily tasks, work, and social and leisure activities. Two recent studies – EMBLEM[13] in Europe and UNITE,[14] a global survey of patients – underscore high rates of work impairment, with a majority unable to maintain full-time employment. Perhaps not surprisingly in light of these difficulties, a meta-analysis of 19 between-group comparisons (N= 1838) by Nilsson et al[15] showed that self-esteem in patients is low, even

[a] See the subsection on classification under Foundations of Management for definitions of BD-I and BD-II.

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CANMAT – or the Canadian Network for Mood and Anxiety Treatments – is a federally incorporated academically based not-for-profit research organization with representation from multiple Canadian universities. The ultimate goal of CANMAT is to improve the quality of life of persons suffering from mood and anxiety disorders, through conduct of innovative research projects and registries, development of evidence based and best practice educational programs and guideline/policy development.

during remission, suggesting a specific psychotherapy target. Furthermore, BD patients are at markedly elevated risk of suicide.[16-20] A meta-analysis of 15 studies by Novick et al[16] determined prevalence rates of attempted suicide of 36.3% in BD-I and 32.4% in BD-II. All of these factors underscore the complexity and chronicity of BD, mandating the need for a systematic chronic disease-management model applied by a multidisciplinary healthcare team. All versions of the CANMAT guidelines, up to and including the 2013 update,[21] have emphasized the need for coordinated and multimodal treatment, with emphasis on the foundations of management as a prerequisite to treatment of phases of BD.

Foundations of Management

Classification and diagnosis

BD is divided into 3 main categories.[22,23] BD-I is characterized by the occurrence of at least one full manic episode, regardless of whether depression has been experienced (although most people with BD-I do experience depression). In contrast, BD-II is typified by a primary symptom presentation of recurrent depression accompanied by hypomanic episodes. Finally, bipolar conditions not elsewhere classified, previously called BD not otherwise specified (NOS), represents disorders with manic/hypomanic symptoms that do not meet criteria for the defined BD subtypes, such as mood elevations with too few symptoms or of an insufficient duration for hypomania. In all cases, to be considered BD, these presentations must be exclusively secondary to substance use, a medical condition, or a concomitant psychiatric disorder.

The new *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) features separate sections on BD and related conditions, and depressive disorders.[22,24] A major change is in Criterion A for manic and hypomanic episodes, which now includes an emphasis on changes in activity/energy and not just mood. Also, the DSM-IV category of a "mixed episode" as an independent entity has been dropped; instead, episodes are characterized as either manic, hypomanic, or depressive, with a specifier of "with mixed features" added if significant symptoms of the opposite pole are present. An additional specifier also allows rating of concomitant anxiety symptoms.

Adherence to existing guidelines for the accurate identification and differential diagnosis of BD rather than by heuristic means is an effective method for avoiding misdiagnosis.[25-27] Histories from family, caregivers, and/or friends are typically helpful in providing collaborative or confirmatory details towards the diagnosis. As well, manualized diagnostic interviews such as the Structured Clinical Interview for DSM-IV (SCID)[28] and the Schedule for Affective Disorders and Schizophrenia (SADS),[29] and screening tools such as the General Behavior Inventory[30] or the Mood Disorder Questionnaire[31] are important steps in a complete assessment. Patient diaries are also useful means of gathering diagnostic information.

A key confounder is the high prevalence of other medical or psychiatric disorders, either as the underlying causes of bipolar-like symptoms or as comorbidities with BD. Anxiety, personality, and substance-use disorders are the most common comorbid psychiatric conditions, and on their own can mimic BD symptoms. The overlap in symptoms often leads to misdiagnosis.[32-34] For example, changes in energy, sleep, and/or irritability are characteristic of a variety of disorders in addition to BD, underscoring the importance of careful differential diagnosis.

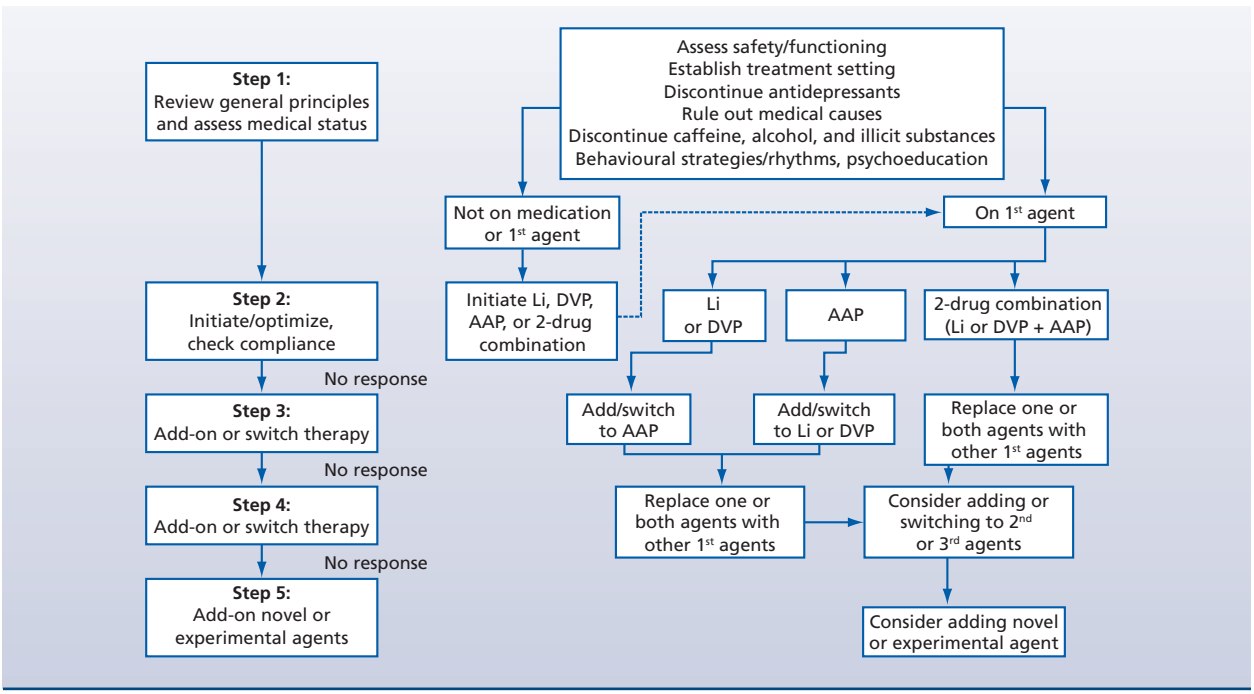
Acute Management of Bipolar Mania

Episodes of mania and hypomania are the hallmarks of BD. Interpretation of the typically agitated state of an acute manic episode is a diagnostic and therapeutic challenge. Mania may be pure or mixed; ie, mania with intercurrent depressive symptoms.[24] Psychotic symptoms (eg, hallucinations or delusions) may or may not be present. The patient may also have a history of rapid cycling.

An agitated and/or aggressive presentation requires initial emergency assessment and management. The CANMAT treatment algorithm for acute mania is shown in Figure 1.[21] Pharmacotherapy in acute mania is supported by several meta-analyses.[35-37] First-line monotherapy options remain the mood stabilizers lithium and divalproex, and the atypical antipsychotics risperidone, olanzapine, standard and extended-release (XR, ER) quetiapine, ziprasidone, and aripiprazole. The 2013 update added divalproex ER, asenapine, and paliperidone ER as other recommended first-line agents. Certain clinical features may guide medication choices in individual patients. For example, lithium may be more effective in cases of classic euphoric mania, while mixed episodes or a history of rapid cycling may favour divalproex. Atypical antipsychotics may be more effective in mixed mania and are particularly favoured when agitation or psychosis is present. Also remaining as first-line therapy is a combination of a mood stabilizer and an atypical antipsychotic, which has been demonstrated to provide more rapid efficacy with approximately 20% higher response rates than with a mood stabilizer alone.[38] Asenapine was added to the atypical antipsychotic combination options, further to the publication of results of a 40-week extension to a 12-week randomized, controlled trial (RCT) demonstrating significant improvement in mania symptoms versus placebo in patients receiving lithium/divalproex.[39] Nonresponse to a 2-week trial of any of the above agents should prompt a switch to another first-line agent or the addition of a second first-line medication. Several first-line options should be tried before moving to a second-line agent; use of concomitant clonazepam is also frequently helpful.

In the 2013 update, haloperidol was added to previous second-line monotherapy options carbamazepine (standard and ER) and electroconvulsive therapy (ECT); the change of haloperidol from third- to second-line therapy is further to a meta-analysis by Cipriani et al,[35] which found that haloperidol had the largest effect size in the treatment of acute mania. Second-line combination therapy remains lithium + divalproex. Third-line options, intended for treatment-refractory patients, include the addition of cariprazine as monotherapy, as well as chlorpromazine, clozapine, and oxcarbazepine; however, cariprazine has not been approved by Health Canada. The 2013 update also recommends consideration of novel/experimental agents, such as zotepine, levetiracetam, phenytoin, mexiletine, Ω-3 fatty acids, calcitonin, rapid tryptophan depletion, allopurinol, amisulpride, folic acid, and memantine.

Figure 1: Treatment algorithm for acute mania



Li = lithium; DVP = divalproex; AAP = atypical antipsychotic

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Management of Acute Bipolar I Depression

Depression in BD is significantly more common than mania, and BD patients are much more likely to seek medical care during a depressive than a manic episode.[40] Kupka et al[41] determined depression/mania ratios of 2.9 and 3.8 for BDI and BDII, respectively. Bipolar depression also has a more profound impact on patients, in terms of duration and quality of life, than manic episodes.[40]

The CANMAT recommendations for management of bipolar I depression are shown in Table 1.[21] There were no changes since the 2009 update to the lists of first-line monotherapies – lithium, lamotrigine, and quetiapine (standard and XR) – or to first-line combination therapy (lithium or divalproex + a selective serotonin receptor inhibitor [SSRI], olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion); paroxetine should not be used in the aforementioned combinations as the SSRI component. As with bipolar mania, there is evidence to suggest that a lack of early (2-3 weeks) response is sufficient to consider switching therapies.

For second-line therapy, lurasidone joined divalproex as monotherapy; also new was the use of either lurasidone or lamotrigine as a combination option with lithium or divalproex. Adjunctive modafinil and quetiapine + a SSRI remain second-line combination options. Lurasidone in initial studies has been shown to be effective in bipolar depression as both monotherapy and adjunctive therapy but the lack of clinical experience and lack of the final published versions of key registration studies at the time of writing of the CANMAT guidelines precluded assigning lurasidone as a first-line treatment.[42,43] Monotherapies in third-line options remained mostly the same: carbamazepine, olanzapine, and ECT. Importantly, additions to the "not recommended" category included adjunctive levetiracetam and ziprasidone, either monotherapy or adjunctive. This update echoes previous guideline versions in identifying ECT as a potential choice for first- or second-line use in select cases, particularly psychotic bipolar depression, high suicide risk, and medical complications secondary to not eating or drinking.[21] Two recent trials of ECT add support to its effectiveness in BD patients; of note, BD patients on anticonvulsants fared well with ECT but required more sessions of ECT than BD patients not on anticonvulsants.[44,45] Additional recommendations of third-line strategies include combinations include lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + a monoamine oxidase inhibitor (MAOI), and lithium or divalproex or an atypical antipsychotic + a tricyclic antidepressant. Finally, the guidelines include a nuanced discussion of the controversies in the use of antidepressants for bipolar depression, suggesting the brief use of most SSRIs or bupropion with a concomitant mood stabilizer, and the avoidance of paroxetine, venlafaxine, and tricyclics.

Maintenance Therapy

The remission-relapse nature of BD underlines the importance of maintenance therapy, and it is this phase in which psychotherapy has a critical role, as summarized below. Factors associated with time to relapse include medication adherence, presence of subsyndromal symptoms, baseline psychosocial stress, higher number of prior episodes, BD-II versus BD-I, female gender, recent substance abuse, and rapid cycling.[46-48] Relapse is often linked to medication nonadherence, which the guidelines indicate has been shown to be associated with a high frequency of bipolar episodes (especially depressive), increased

Table 1: Recommendations for pharmacological treatment of acute bipolar I depression[a]

First line	
Monotherapy	Lithium, lamotrigine, quetiapine, quetiapine XR
Combination therapy	Lithium or divalproex + SSRI[b], olanzapine + SSRI[b], lithium + divalproex, lithium or divalproex + bupropion
Second line	
Monotherapy	Divalproex, *lurasidone*[c]
Combination therapy	Quetiapine + SSRI[b], adjunctive modafinil, *lithium or divalproex + lamotrigine*[c], *lithium or divalproex + lurasidone*[c]
Third line	
Monotherapy	Carbamazepine, olanzapine, *ECT*[d]
Combination therapy	Lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI[b] + lamotrigine, *quetiapine + lamotrigine*[c]
Not recommended	
Monotherapy	Gabapentin, aripiprazole, *ziprasidone*[c]
Combination therapy	*Adjunctive ziprasidone*[c], *adjunctive levetiracetam*[c]

ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

[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] Except paroxetine.

[c] *New or change to recommendation.*

[d] Could be used as first- or second-line treatment in certain situations

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hospitalization and emergency room visits, and more work absences. The literature reports adherence rates to prescribed medication in the range of 70% to as low as 31%.[49-53] Factors that increase nonadherence include lack of understanding or awareness of BD, side effects (SEs), inadequate treatment efficacy, irregular daily routine/living circumstances, difficulties with medication routines, depressive polarity of the last acute episode, concomitant substance abuse, and belief by the patient that medications are no longer necessary. Complications with SEs relate to both actual SEs experienced by patients (real or imagined) and fear of perceived SEs. Sedation and weight gain were among the most significant SEs connected with reduced adherence.[49]

There were no changes in first-line maintenance therapy options: lithium, lamotrigine (effective only in preventing relapse into depression), divalproex, olanzapine, quetiapine, long-acting injectable (LAI) risperidone, and aripiprazole. First-line combinations remain adjunctive lithium or divalproex + quetiapine, LAI risperidone, aripiprazole, or ziprasidone. Evidence remains strong for lithium, lamotrigine, olanzapine, and (to a lesser degree) divalproex. An evidence gap exists in the maintenance phase as most RCTs are ≤1 year, with none longer than 2 years. Nonetheless, 2 meta-analyses[54,55] summarize existing data to demonstrate efficacy of the first- and second-line maintenance treatments in the CANMAT guidelines.

For second-line treatment, paliderido ER is added to carbamazepine as monotherapy. Combination therapy remains unchanged from the 2009 update: lithium + one of divalproex, carbamazepine, olanzapine, risperidone, or lamotrigine, divalproex + olanzapine, and olanzapine + fluoxetine. The new option for third-line therapy is asenapine, both as monotherapy and adjunctive therapy, which was added on the basis of newly published data showing benefit.[56,57] Other adjunctive choices include phenytoin, clozapine, ECT, topiramate, Ω-3-fatty acids, oxcarbazepine, and gabapentin.

Psychotherapy

The literature has historically supported the benefit of psychological interventions – including psychoeducation, cognitive behavioural therapy (CBT), family therapy, and interpersonal and social rhythm therapy – in combination with pharmacotherapy. Lam et al[58] concluded that psychotherapies were effective in the prevention of or delay in relapse (overall relative risk 0.74; 95% confidence interval 0.64–0.85). Several studies have provided conflicting data on the value of CBT for BD;[59-62] however, 2 other studies[63,64] have highlighted the value of psycho-education either alone or as a component of CBT, with striking cost-effectiveness for group psychoeducation noted.

Psychoeducation should be delivered when the diagnosis of BD is first made, but needs periodic, brief reiteration and reinforcement; a full repeat (years after the diagnosis) of a psychoeducational program with emphasis on a relapse prevention drill is often useful.

Acute and Maintenance Management of Bipolar II Disorder

As stated previously, BD-II is characterized by the phenomenology of depression and hypomanic episodes; the former, either syndromal or subsyndromal, is the prominent feature of BD-II.[22,23] BD-II is believed to be the more prevalent form, and rapid cycling may be more common than in BD-I.[23,65,66] The lack of well-designed studies on BD-II poses a barrier to the development of evidence-based recommendations for hypomania; thus, current guidelines rely on extrapolation of effective therapies for mania based on accumulated clinical experience.

There were few changes in the updated guideline recommendations for the treatment of acute BD-II depression. Quetiapine remains the only first-line monotherapy; the XR version is added to the standard form. Second-line therapy is identical to the previous update: lithium, lamotrigine, divalproex, lithium or divalproex + antidepressants, lithium + divalproex, and atypical

antipsychotics + antidepressants. The new options for third-line care include quetiapine + lamotrigine and adjunctive ECT, N-acetylcysteine or triiodothyronine, which were added to antidepressant monotherapy (primarily for those with infrequent hypomanias) and alternate antidepressants.

For maintenance therapy in BD-II, quetiapine was added to existing first-line options lithium and lamotrigine. Adjunctive quetiapine and lamotrigine are the new elements in second-line therapy, joining divalproex, combination lithium or divalproex or atypical antipsychotic + antidepressant, and combination of 2 of lithium, divalproex, or an atypical antipsychotic. Fluoxetine is the latest third-line option with carbamazepine, oxcarbazepine, atypical antipsychotics, and ECT.

Conclusion

The 2013 update to the CANMAT guidelines both re-emphasizes the essential diagnostic and management approaches to the significant global health issue of BD and provides important new therapeutic options for its various components and presentations. Therapies must be tailored to the individual patient, optimally with pharmacological and psychotherapeutic components and with ongoing regular comprehensive patient assessment to maximize outcomes and safety. Due to limitations of space, this newsletter only summarizes the sections on foundations of management as well as treatment of each phase of BD. The full 2013 guidelines update includes valuable additional sections on special populations such as women, children, and the elderly, on bipolar II, and on metabolic monitoring. The full article, along with earlier versions of the guidelines, may be downloaded from the CANMAT website at www.canmat.org.

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Dr. Parikh has received honoraria or research or educational conference grants in the past 2 years from AstraZeneca, Bristol-Myers Squibb, CIHR, CANMAT, Canadian Psychiatric Association, Eli Lilly & Co., Lundbeck, Mensante, and Pfizer. Dr. Goldstein has received investigator-initiated research support from Pfizer and has served as a speaker for Purdue Pharma.

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