Summary: Treatment of Bipolar Disorder

Roger S. McIntyre, M.D., FRCPC
Professor of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada
Board Chair, Depression and Bipolar Support Alliance (DBSA) Board of Directors, Chicago, Illinois, USA

Introduction

Bipolar disorders (BD) are a group of severe lifelong disorders that are associated with staggering loss of human capital, loss of healthy living years as well as lifespan. Although mania is the defining feature of bipolar I disorder, and hypomania with at least one depressive episode defining bipolar II disorder, it is well-established that depressive symptoms and episodes are the predominant illness presentation. The predominance of depressive symptoms across bipolar subtypes is apparent not only at the first illness presentation but also along the longitudinal course.

An unmet need in bipolar disorder remains the staggering misdiagnosis rate and the delay in determining that the diagnosis is present. This prolongs human suffering, increases morbidity and mortality, service utilization, healthcare costs and necessarily fosters progression of the illness. As most individuals with bipolar disorder are initially incorrectly diagnosed, treatment selection is often inappropriate, further promoting negative health outcomes.

The predominance of depression in bipolar disorder and high misdiagnosis rate provides the impetus for routine screening for bipolar disorders in all persons initially presenting with depression and for subsequent visits if characteristics of bipolar disorder become manifest and/or response to treatment is inadequate. A quantity of screening tools for bipolar disorder exist which differ in their items, psychometrics, time to completion and feasibility in busy clinical practice. The Rapid Mood Screener (RMS; https://www.rapidmoodscreener.com/) has been recently validated as a brief, validated screening tool with validation completed and satisfactory psychometrics in adults with bipolar I and bipolar II disorder. The RMS has improvements in psychometrics in time to administration as well as end-user satisfaction relative to other screening tools for bipolar disorder.

Principles of Treatment

The use of measurement to track symptoms (e.g., mood diaries) is encouraged and attempts to prevent comorbidities should be a clinical focus at initial presentations. Recognition that BD is an independent risk factor for cardiovascular disease further underscores the importance of holistic approaches to the assessment, prevention, and management of BD. Individuals with BD report much higher rates of physical and sexual trauma in the recent or distant past as well as describe psychosocial stressors as associated with episode recurrence. In addition to targeting key features of BD, the management of BD also needs to include psychoeducation, improvement of diagnosis and treatment literacy, conflict and stress management skills, as well as lifestyle improvement with focus on diet as well as sleep hygiene.

Pharmacologic Treatment of Acute Bipolar Mania/Mixed States

The pharmacologic treatment of acute bipolar mania/mixed states has been augmented with the combination of olanzapine-samidorphan. Olanzapine-samidorphan combination is FDA-approved for the treatment of acute mania/mixed states in adults with bipolar I disorder as monotherapy or adjunct to lithium or valproate. It was the panel's view that olanzapine-samidorphan would be prioritized ahead of olanzapine in the treatment of acute mania or mixed states as monotherapy or adjunct to lithium or valproate due to a lower

weight gain liability of olanzapine-samidorphan relative to olanzapine. Moreover, available evidence indicates that although samidorphan mitigates weight gain liability attributable to olanzapine, it does not mitigate olanzapine's efficacy.

Pharmacologic Treatment of Acute Bipolar Depression

The panel recommends cariprazine, lumateperone and lurasidone monotherapy as initial treatment for bipolar I depression. Lumateperone and lurasidone are also approved as adjuncts to lithium or valproate in bipolar I depression. Lumateperone is additionally approved as monotherapy or adjunct to lithium or valproate in the treatment of bipolar II depression. Quetiapine is approved as monotherapy in bipolar II depression but not as adjunctive treatment. The panel recognizes that cariprazine, lumateperone and lurasidone have lower propensity to weight gain and are metabolically similar to placebo in the treatment of adults with BD. These observations differentiate these second-generation antipsychotics (SGAs) from quetiapine and olanzapine-fluoxetine combination which have greater susceptibility to clinically significant weight gain and/or metabolic shift. It was the view of the panel that consideration of weight gain and metabolics is paramount in selecting treatments for bipolar depression. The panel also recommends lithium or lamotrigine as possible first-line treatments for bipolar depression. The anti-suicide effects of lithium, not seen with other FDA-approved treatments for BD, are an important attribute of lithium.

The panel recognizes that antidepressant monotherapy in bipolar I disorder is to be discouraged. Conventional antidepressants are not recommended in bipolar I disorder for adults manifesting mixed features, rapid cycling, and/or histories of previous antidepressant-associated emergence of hypo/mania. For adults with bipolar II disorder, preliminary evidence suggests that some adults may be safely and effectively treated with antidepressant monotherapy. Antidepressant monotherapy however would not be recommended for persons with bipolar II disorder presenting with mixed features, rapid-cycling and/or history of antidepressant-associated affective switching/cycle acceleration/dysphoria. The lack of empirically supported response predictors to antidepressant monotherapy in BD implies that it is unknown *a priori* which individuals with bipolar II disorder may be safely treated with antidepressant monotherapy. The panel also recognizes that there is a paucity of long-term treatments with antidepressants in BD. The recommendation to continue antidepressants will be determined on an individual basis.

The ***2023-2024 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*** has retained similar guidance with respect to pharmacologic treatments of bipolar mania. Bipolar mania is recognized as a medical emergency requiring, in many cases, a higher intensity of treatment. Safety is of paramount importance of mania and, where applicable, inpatient stay and specialist consultation is encouraged. The panel also recognizes that for many adults with bipolar mania, the predominant presentation is dysphoric and mixed with many adults manifesting non-specific symptoms (e.g., anxiety, agitation, irritability, anger) that often obscure the underlying diagnosis of mania. SGA monotherapy as well as lithium or divalproex are recommended in cases of mania of milder severity (e.g., non-psychotic mania). In situations where patients have severe mania (e.g., psychosis, need for hospitalization), combination SGA and additional mood stabilizing agent (e.g., lithium) is recommended.

Maintenance Pharmacological Treatment of Bipolar Disorder

More than 90% of individuals with BD will experience recurrence of illness. Episode recurrence in BD is highly associated with progressive changes to brain structure and function, as well as the accumulation of multiple comorbidities. Further evidence also suggests that greater episode frequency is associated with more pronounced cognitive deficits in BD. Moreover, it is not frequent in BD to witness a phenomenological shift across time where patients manifest increasing depressive symptom burden. A clinical impression awaiting cogent empirical confirmation is that, increasingly, clinicians are encountering a higher percentage of individuals with BD presenting with mixed features during the acute or maintenance phase. It is uncertain what is causing this, but, certainly, antidepressant utilization, drug and alcohol misuse and obesity are contributing causes.

The combination of olanzapine-samidorphan has been approved as a maintenance monotherapy in adults with bipolar I disorder. The approval of olanzapine-samidorphan was based on legacy studies in maintenance treatment of bipolar disorder with olanzapine. The combination of olanzapine-samidorphan exhibits a lower propensity to weight gain and waist circumference enlargement when compared to olanzapine when studied in adults with schizophrenia. It was the panel's view that a lower weight gain liability with olanzapine-samidorphan relative to olanzapine would prioritize olanzapine-samidorphan over olanzapine in the selection sequencing of maintenance treatments in bipolar disorder.

For most adults with BD, multi-year/lifetime pharmacotherapy is recommended, integrated with lifestyle interventions targeting healthful living, diet, exercise, and sleep hygiene. For many adults, manual-based psychosocial treatments (e.g., cognitive therapy), interpersonal social rhythm therapy and psychoeducation, are critical adjuncts to pharmacotherapy to improve overall psychosocial function and wellbeing. During the acute and maintenance phase of BD, careful attention to suicidality is paramount.

References:

1. McIntyre RS, Patel MD, Masand PS, et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. Curr Med Res Opin 2021;37(1):135–44.
2. Thase ME, Stahl SM, McIntyre RS, et al. Screening for Bipolar I Disorder and the Rapid Mood Screener: Results of a Nationwide Health Care Provider Survey. Prim Care Companion CNS Disord [Internet] 2023;25(2). Available from: http://dx.doi.org/10.4088/PCC.22m03322
3. McIntyre RS, Alda M, Baldessarini RJ, et al. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry 2022;21(3):364–87.
4. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet 2020;396(10265):1841–56.