

Summary for Treatment of Bipolar Disorder *(continued)*

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INTRODUCTION

Bipolar disorder (BD) is a severe, lifelong group of disorders with an estimated prevalence of approximately 2%. Approximately three-quarters of individuals with BD exhibit features of the disorder prior to the age of 25 highlighting the neurodevelopmental aspects of the disorder as well as the importance for screening and timely diagnosis, especially in younger populations presenting in clinical settings with clinically significant depressive and anxiety symptoms. Misdiagnosis representing a conflation of both false positives and false negatives continue to be one of the greatest unmet needs in BD. The consequences of missed and delayed diagnosis are protean and include the accumulation of comorbidities (e.g., obesity, substance abuse), unmitigated suicide risk, erroneous treatment selections, human suffering, and increased morbidity.

The panel agreed that screening for BD is essential for any person presenting with mood related symptoms and/or in clinical scenarios wherein conventional treatments for a mood disorder are inadequate. Results from longitudinal studies consistently report that most individuals with BD exhibit depression, depressive symptoms, and/or episodes as the predominant presentation of the illness as well as polarity at first presentation. Consequently, many adults with BD transition from the diagnosis of Major Depressive Disorder (MDD) to BD over multiple years of prospective follow-up. For example, it is reported that approximately 1% of adults with “MDD” transition to BD annually underscoring the importance of vigilance for hypo/manic presentations in adults originally diagnosed with having MDD.

In addition to misdiagnosis as well as delayed diagnosis, insufficient attention to comorbidity in BD is identified as an unmet need. Adults with BD are affected by a large number of medical and mental comorbidities with at least half of patients meeting criteria for three or more concurrent conditions. It is not uncommon for the comorbid conditions to be a phenomenological antecedent to BD and, not infrequently, obscuring the underlying diagnosis of BD.

Similar to adults with MDD, it is recognized that the vast majority of adults with BD are not achieving full syndromal and functional recovery. This deficiency is in part explained by inadequate/inappropriate treatments, treatment non-concordance, as well as insufficient attention to comorbidities and relevant psychosocial factors. It is additionally recognized that for a substantial population of adults with BD, enduring deficits across multiple domains of cognitive function remain a source of distress and mediator of functional impairment. In some cases, the severity, persistence, and complexity of cognitive impairment in BD phenotypically mimics attention deficit hyperactivity disorder (ADHD). Hitherto, there are no United States Food and Drug Administration (FDA)-approved treatments for cognitive dysfunctions in BD nor are there any evidence-based and proven treatments for cognitive impairment in BD.

Results from the extant literature indicate that outcomes in BD are optimal when individuals are diagnosed timely and accurately and receive guideline-informed measurement based, integrated, and multidisciplinary care. For individuals with treatment-resistant BD, evidence also supports cognitive and functional remediation as a manual-based intervention. Response rates to conventional treatments for BD, both pharmacologic and psychosocial, are diminished

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in subpopulations with higher episode frequency. Moreover, populations with greater episode frequency exhibit greater susceptibility to additional disorders including, but not limited to, cardiovascular disease, obesity, and dementia.

PRINCIPLES OF TREATMENT

The unmet need regarding timely and accurate diagnosis instantiates the importance of using screening tools (e.g., Mood Disorder Questionnaire; MDQ) in adults with BD. Screening should take place at initial assessments and any scenarios wherein inadequate outcomes are being observed. Screening does not supplant a careful and comprehensive clinical evaluation which is sine qua non to establishing the diagnosis of BD. 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 DEPRESSION

The panel recommends cariprazine and lurasidone monotherapy as initial treatment for bipolar depression. Lurasidone is also recommended in combination with lithium or divalproex. The panel recognizes that lurasidone is not FDA-approved for mania; cariprazine and quetiapine are approved for acute bipolar mania/mixed states. Cariprazine was FDA approved in 2019 for the acute treatment of bipolar depression. The panel recognizes that cariprazine 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 are susceptible 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. 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.

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PHARMACOLOGIC TREATMENT OF ACUTE BIPOLAR MANIA

The **2019-2020 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. 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. Is obesity changing the phenotype of bipolar disorder from predominately euphoric toward mixed presentations? *Bipolar Disord.* 2018 Dec;20(8):685–6.
2. Burdick KE, Millett CE, Bonnín CDM, Bowie CR, Carvalho AF, Eyster LT, et al. The International Consortium Investigating Neurocognition in Bipolar Disorder (ICONIC-BD). *Bipolar Disord.* 2019 Feb;21(1):6–10.
3. Altshuler LL, Sugar CA, McElroy SL, Calimlim B, Gitlin M, Keck PE Jr, et al. Switch Rates During Acute Treatment for Bipolar II Depression With Lithium, Sertraline, or the Two Combined: A Randomized Double-Blind Comparison. *Am J Psychiatry.* 2017 Mar 1;174(3):266–76.