Pharmacological Treatment of Bipolar Disorder: 2017-2018 Update Summary

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Introduction

Bipolar disorders (BD) are associated with high rate of non-recovery, inter-episodic dysfunction, and chronicity. Mortality studies indicate that the rate of premature mortality is significantly elevated in bipolar disorder with a widening chasm in the mortality rate between affected individuals and persons in the general population. Convergent and replicated evidence indicates that utilization of a chronic disease model is an integral component to improving health outcomes in bipolar disorder, with salutary effects on both morbidity and mortality outcomes. Moreover, by improving precision, consistency, and appropriateness of treatment selection, decision support with evidence informed guidelines have demonstrated to reduce both individual and societal costs attributable to bipolar disorder.

The update of the ***2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*** represents the most up-to-date treatment recommendations and decision support for multiple stakeholders involved with, and who provide care for, individuals diagnosed with bipolar disorder. This current iteration provides a further refinement, in some cases differential emphasis, from the previous published version (Ostacher, Tandon, and Suppes 2016). In contradistinction from most treatment guidelines in bipolar disorder, the *2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* represents a synthesis of evidence and multi-disciplinary opinion from multiple stakeholders, including, but not limited to academicians, clinicians, and experts in private and public healthcare policy. The current portrait sketched of bipolar disorder as a common, complex, and lifelong disorder that significantly curtails human capital invites the need for multi-disciplinary consensus on pragmatic and scalable interventions. The updated version of the *2017-2018 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults* provides an update of pharmacologic, psychosocial, and neurostimuatory treatment approaches for symptom management.

Principles of Treatment

There are several guiding principles of treatment that are emphasized in the 2017-2018 guidelines. A particular emphasis is made on the importance of timely and accurate diagnosis. It remains a modifiable deficiency in bipolar disorder that the majority of affected individuals continue to be misdiagnosed and/or diagnosed long after observable characteristics and service utilization related to bipolar disorder have appeared. Safety assessment continues to be a priority and guiding principle in bipolar disorder, with emphasis not only on suicide and risk reduction, but also an urgency given to risk factor modification for common and chronic non-communicable comorbid physical health conditions (e.g., cardiovascular disease, metabolic syndrome). A third guiding principle is the importance of careful calculus of benefit of treatment expected compared to the holistic appraisal of treatment-related side effects and safety concerns. It is the view of the

authorship of the guideline, that collective treatments for acute-based management (i.e., acute mania, acute bipolar depression) need to anticipate both short- and long-term side effects and safety concerns (e.g., weight gain). Priority is always given to safe, well-tolerated treatments that are supported by rigorous, randomized, double-blind, placebo-controlled trials.

Moreover, the guiding principle of integrating multimodality treatments in bipolar disorder is emphasized in light of the evidence supporting and the rationale for considering manualized-based psychosocial treatments (e.g., cognitive behavioral therapy, interpersonal social rhythm therapy). The 2017-2018 guideline further presses the principle on the importance of giving equal priority to somatic health (e.g., cardiovascular disease) as is given to conventional treatment targets in bipolar disorder (e.g., mania, sleep, cognitive impairment). Finally, patient health management, locus of care (e.g., medical home), and the importance of functional recovery and positive mental health and resiliency, are emphasized.

Pharmacological Treatment of Acute Bipolar Depression

Bipolar depression is the predominant therapeutic target in bipolar disorder in most early and later phases of the illness. Furthermore, depressive symptoms as part of bipolar disorder are often chronic, and highly associated with risk, comorbidity (e.g., cardiovascular disease), functional impairment, and suicidality. The United States Food and Drug Administration (FDA) has approved three psychotherapeutic agents of bipolar depression (i.e., lurasidone, quetiapine, and olanzapine-fluoxetine combination). The expert panel for the Florida Guidelines consensually agree to also list lamotrigine as a possible first-line treatment strategy in bipolar depression. The expert panel recognizes that lamotrigine has not received regulatory approval for marketing in bipolar depression. Notwithstanding, results conducted in large academic centers, as well as meta-analyses, indicate that lamotrigine is an effective agent for both acute and recurrence prevention of bipolar depression (lamotrigine is currently FDA-approved for recurrence prevention in bipolar disorder). Cariprazine, a D3 preferring D2/D3 partial agonist is currently approved for mania and mixed states in bipolar disorder, but not for bipolar depression. At the time of completing the 2017-2018 Florida Guidelines, results from two pivotal registration trials in adults with bipolar I depression indicate that cariprazine is efficacious in the acute treatment of bipolar I depression. The 2017-2018 guidelines re-emphasize the ubiquity and hazards posed by mixed features in bipolar disorder. Hitherto, no safe and reliable treatment is unequivocally established and efficacious in mixed bipolar depression (McIntyre, 2017). Notwithstanding, select atypical antipsychotics are likely the initial treatments of choice for many individuals with bipolar depression and mixed features. Select second generation antipsychotics are also recommended as first-line treatment for mania with mixed features.

Antidepressant utilization remains an understudied and controversial issue in bipolar disorder. No single antidepressant or class of antidepressants are approved for bipolar disorder. It is recognized by the Florida Expert Panel that antidepressants continue to be utilized at a high rate in adults with bipolar disorder. The guiding principle of utilizing antidepressants in bipolar disorder is that they should not be prioritized over better established and FDA-approved treatment, and should be utilized as adjunctive treatment strategies. The use of antidepressant monotherapy is highly discouraged in bipolar I disorder, while the safe and effective use of antidepressants in bipolar II disorder remains a possibility, but still requires replicated empirical evidence. Psychosocial treatments, like pharmacotherapeutic treatments for bipolar disorder, are recognized to be more effective earlier in the illness course. For treatment-resistant bipolar depression, electroconvulsive

therapy (ECT) remains the recommended treatment option, with evidence also supporting alternate neurostimuatory approaches (e.g., rTMS).

Pharmacological Treatment of Acute Bipolar Mania

The expert panel recognizes that mania is not only a defining feature of bipolar I disorder, but is a medical emergency requiring urgent detection, establishment of safety, appropriate setting assignment for care, and evidence-based treatments. No substantive changes were made to the acute mania guidelines when compared to the 2015 iteration, with an ongoing emphasis on FDA-approved second-generation antipsychotics, lithium, and divalproex, as the most commonly recommended first-line strategies.

Continuation and Maintenance Pharmacological Treatment of Bipolar Disorder

Bipolar disorder is a highly progressive condition, as evidenced by greater episode frequency, duration, and complexity, as well as diminished treatment response across the illness trajectory. It is also recognized in bipolar disorder that best practices utilizing integrated multimodality therapies reduce and forestall risk of recurrence, and speculatively, neurobiological progression and cumulative illness load. Since the publication of the 2015 guidelines, the FDA has approved aripiprazole long-acting injectable (LAI) as a recurrence prevention treatment in bipolar disorder. The FDA has also approved aripiprazole proteus (Abilify MyCite®), which may be extrapolated to the bipolar population. Aripiprazole proteus (Abilify MyCite®) is a combination product comprised of oral aripiprazole embedded with an ingestible digital sensor to record and communicate medication ingestion events. Whether digital sensory detection improves compliance and health outcomes in bipolar disorder, however, is not well known. As per the previous guidelines, key therapeutic targets during long-term treatment of bipolar include subsyndromal depression, affective instability, cognitive impairment, sleep disturbance, comorbidity (e.g., substance use disorder, anxiety disorder, cardiovascular disease, obesity), as well as interpersonal, social and workplace dysfunction (Miskowiak et al., 2017). Multimodality interventions incorporating pharmacotherapy, psychosocial treatment, cognitive remediation, lifestyle modification (e.g., exercise), are critical components of long term care. As with major depressive disorder (MDD), it is also recommended by the expert panel that advocacy, for example, the Depression and Bipolar Support Alliance (DBSA), can play a critical role in education support service access and illness/treatment literacy and should be considered an integral component of care for any person affected by bipolar disorder.

References:

McIntyre, Roger S. 2017. "Mixed Features and Mixed States in Psychiatry: From Calculus to Geometry." CNS Spectrums 22 (2):116–17.

Miskowiak, K. W., K. E. Burdick, A. Martinez-Aran, C. M. Bonnin, C. R. Bowie, A. F. Carvalho, P. Gallagher, et al. 2017. "Methodological Recommendations for Cognition Trials in Bipolar Disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force." Bipolar Disorders 19 (8):614–26.

Ostacher, Michael J., Rajiv Tandon, and Trisha Suppes. 2016. "Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Bipolar Disorder: A Novel, Practical, Patient-Centered Guide for Clinicians." The Journal of Clinical Psychiatry 77 (7):920–26.