Pharmacological Treatment of Bipolar Disorder: 2015 Update Summary

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INTRODUCTION

Discrepancies between health outcomes achieved in the clinical ecosystem and those achieved in research settings is a disquieting and modifiable deficiency in the management of adults with bipolar disorders. The 2015 iteration of the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults (6th update) is a critical component of decision support that attempts to narrow the foregoing gap in health outcomes by fostering precision and consistency, as well as the appropriate selection and sequencing of treatments throughout each stage of the illness. In the interest of consistency from the previous edition of the guidelines, we have retained the three algorithms for acute mania, acute bipolar depression, and bipolar continuation/maintenance with the recognition that for many individuals with bipolar disorder, the illness is highly relapse-prone, chronic in nature, and lifelong.

Since the publication of the adult guidelines fifth edition in 2013, there has been only one new U.S. Food and Drug Administration (FDA)-approved agent (i.e., cariprazine for acute bipolar mania) for any phase of bipolar disorder. Notwithstanding, there has been robust and accumulating evidence for greater attention given to clinical aspects of chronobiology, metabolic and physical health aspects, cognitive dysfunction, as well as premature mortality in this population.

PRINCIPLES OF TREATMENT

Replicated scientific evidence indicates that the misdiagnosis of bipolar disorder occurs in a significant percentage of individuals. Thus, clinicians are encouraged to screen for bipolar disorders among adults utilizing healthcare services for affective and anxiety-related symptomatology at index visit and across repeated visits if therapeutic objectives are not achieved. Vigilance for bipolar disorder is warranted among individuals presenting in healthcare settings with depressive symptoms, as depressive episodes are often “polarity-first” as well as “polarity-predominant” in individuals with bipolar disorder. The timeliness of accurate diagnosis is underscored by convergent evidence in support of an integrated conceptual pathogenic framework indicating that bipolar disorder has both neurodevelopmental as well as neurodegenerative aspects.

In 2015, the American Heart Association consensus statement identified bipolar disorder (and major depressive disorder) as a Tier 2 risk factor for cardiovascular disease and accelerated atherosclerotic illness. Population- and clinical-based data have consistently documented elevated rates of medical disorders (e.g. cardiometabolic) in adults with bipolar disorder. The integrated care of bipolar disorder warrants systematic and routine screening for traditional and emerging risk factors for cardiovascular disease. The foregoing recommendation is a derivative of the morbidity and mortality data directly attributable to medical disorders. As well, emerging evidence indicates that concurrent medical disorders affect the age at onset, presentation, severity of illness, and response to treatment; and therefore, are a reminder that general metabolic disorders may “metastasize” to...
the brain. When medical disorders are present, contemporaneous management of both bipolar disorder and medical/psychiatric comorbidity is critical.

As per previous guideline iterations, all individuals with bipolar disorder must be carefully assessed for ideation/plans of harm to self and others with systematic assessment of risk for suicide. Pharmacotherapy in bipolar disorder is considered a standard of care across all phases of the illness. In addition, psychoeducation, and in some cases, manualized psychotherapy (e.g. cognitive behavioral therapy), careful attention to dietary choices, and physical activity levels, as well as sleep hygiene and chronorhythms is critical. The observation that functional outcomes in bipolar disorder are uncoupled from symptomatic outcomes has shifted attention towards other dimensions/domains of disturbance including, but not limited to, cognitive dysfunction. For multi-episode and late-stage bipolar disorder, functional remediation - which targets interpersonal and social competence, and general cognitive function - is warranted.

**Pharmacological Treatment of Acute Bipolar Depression**

Since the previous guideline publication, there have not been replicated, large randomized controlled trials and/or meta-analyses that would justify a significant alteration in the algorithmic sequence introduced in 2013. There remains a paucity of safe, well-tolerated, and effective agents for the acute phase of bipolar depression. The metabolic hazards of olanzapine justify its recommendation as a Level 2B treatment. Quetiapine, also susceptible to metabolic and weight gain hazards as well as sedation/somnolence, is the only psychotherapeutic agent with replicated evidence of efficacy in bipolar II depression. The rationale for relegating olanzapine + fluoxetine to Level 2B status (e.g., metabolic concerns) may also apply in some circumstances to quetiapine; a decision which should be made on an individual basis. Notwithstanding the introduction of the mixed features specifier, there remains an absence of controlled trial data that have evaluated therapeutic outcomes in adults with bipolar depression and mixed features specifier.

Replicated evidence indicates that armodafinil is insufficiently efficacious in adults with bipolar depression.\(^5\) Results supporting the use of novel and investigational agents (e.g., ketamine, anti-inflammatory agents, and antioxidants) remains a focus of ongoing research and cannot be considered as proven effective and safe in bipolar depression. As per previous iterations, the steps of treatment modality suggested integrate both the likelihood of offering therapeutic benefit as well as safety and tolerability concerns. Data has recently emerged indicating that electroconvulsive therapy (ECT) is superior to pharmacotherapy in treatment-resistant bipolar depression.\(^6\)

**Pharmacological Treatment of Acute Bipolar Mania**

Mania comprises a medical emergency in adults with bipolar I disorder. The principles of safety, risk assessment, capacity determination, and timely diagnosis are critical. The scientific evidence is compelling that lithium and divalproex, as well as atypical agents offer therapeutic benefit in mania. So far, no studies have primarily enrolled individuals meeting criteria for mania with mixed features specifier. The increased risk for additive/multiplicative adverse events warrant recommendations for beginning treatment with monotherapy, recognizing that for some individuals receiving combination therapy (i.e., antipsychotic + mood stabilizer combination) may be superior.
Continuation & Maintenance Pharmacological Treatment of Bipolar Disorder

Lithium continues to have a Level 1A recommendation in bipolar disorder as maintenance. A lack of consensus exists as to the role of continuation/maintenance adjunctive antidepressants, with a pragmatic position that they should be individualized and reserved for scenarios wherein they do not destabilize the longitudinal course and are temporally associated with symptom mitigation during therapy, as well as symptom return when discontinued. Illness progression, chronicity, and non-recovery warrant recommendations for integrated psychosocial approaches early in the illness trajectory. Careful attention to both psychiatric and medical comorbidity is paramount for assuring desired long-term health outcomes. The hazards posed by excess weight gain, directly and indirectly, on bipolar disorder pathology is a critical concern regarding treatment maintenance, as well as risk factor modification and attention given to aspects of healthy lifestyle. Where available, functional/cognitive remediation has the ability to improve outcomes for multi-episode, late-stage illness.7