JNP

Lithium Therapy for Bipolar Disorder

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ABSTRACT

The management of bipolar disorder (BD) may be challenging because of the disease state itself. In addition, the maintenance of the drug level of lithium plays a vital role in preventing acute manic or mixed episodes. This article reviews the drug properties of lithium, the current treatment guidelines for BD, and best practices in monitoring lithium therapy, as well as the characteristics and classification of BD.

Keywords: bipolar disorder, challenges of bipolar disorders, lithium, mania, properties of lithium

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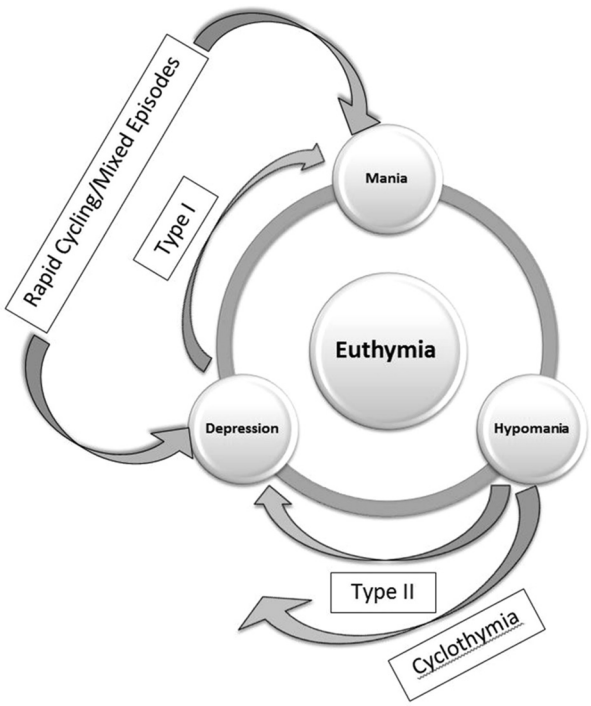
The description of bipolar disorder (BD) may be traced back to the early 19th century,[1] yet the management of this condition remains challenging and complicated even in the present day. The estimated prevalence of BD in the general population is approximately 4%; however, in the primary care setting, it may be as high as 21% to 26%.[2,3] According to the American Psychiatric Association (APA) guidelines, lithium therapy plays a vital role in managing and preventing acute manic or mixed episodes.[4] However, its use has declined in recent years because of the availability of newer atypical antipsychotics, the unacquaintedness of the drug, and the "exaggerated fears" of its toxicities.[5] More recently, the 2016 British Association for Psychopharmacology (BAP) evidenced-based guidelines for treating BD still recommended lithium to be used together with dopamine antagonists or partial agonists for acute breakthrough mania when monotherapy of haloperidol, olanzapine, risperidone, or quetiapine was suboptimal. Additionally, the guidelines suggest lithium to be the most effective therapy in preventing relapse and hospitalization for BD type I.[6] The 2017 International College of Neuropsychopharmacology guidelines also recommended that lithium be considered as first-line therapy during the maintenance phase of BD.[7] In fact, lithium may have neuroprotective properties, which have been reported on multiple occasions. In an animal model, lithium has significantly delayed the onset of status epilepticus in mice when the condition was induced by a pilocarpine injection.[8] Most recently, Berk et al[9] have used structural magnetic resonance imaging to show that lithium was more effective than quetiapine in slowing the reduction of white matter volume after 12 months of therapy. Because of the significant impact of lithium in the treatment of BD, it is prudent for prescribers to understand and be familiar with the properties of this agent and appropriately monitor for therapeutic efficacy and patient safety. This article provides a review of BD and its treatment guidelines. Additionally, it highlights the pertinent characteristics of lithium so prescribers may become more acquainted with this useful agent.

BD OVERVIEW

BD, formerly known as manic-depressive disorder, is characterized by the recurrent episodes of depression and mania. BD may be generally classified into 5 different subtypes depending on the patterns of the episodic depression and mania. Bipolar type I is defined as patients who have at least 1 episode of mania with a minimum duration of 1 week with or without episodes of major depression. Bipolar type II is characterized by the presence of episodes of hypomania accompanied by at least 1 episode of major depression with no psychosis. Cyclothymia involves cyclic periods of 1 or more hypomania and depressive symptoms that do not meet criteria for major depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria. The rapid cycling type describes a condition in which the patients have 4 or more episodes of well-defined

depression or mania during a year. These patients usually have periods of remission for at least 2 months and switch from one to the opposite pole. The mixed episodes type involves patients who have concurrent symptoms of mania and depression. During the manic phase, they also experience at least 2 of the 6 dysphoric symptoms, which include anhedonia, guilt, depressed mood, anxiety, fatigue, and suicidal ideation (Figure). Although BD is defined and recognized during the manic phase, patients with BD commonly present with depression; therefore, patients who have episodes of major depression should also be screened for a history of mania or hypomania.[10] The etiology of BD is primarily genetic in nature. Overexpression of the ankyrin 3 gene has been shown to have a strong association with BD and schizophrenia, especially in the adolescent population. Meanwhile, individuals who have a low-frequency or loss-of-function mutation of this gene are protected against BD or schizophrenia, although the protective effect is stronger with type I than type II BD.[11-13] Furthermore, there may also be some environmental and biological components associated. Other factors such as early childhood abuse and neglect and/or other psychiatric comorbidities may increase the risk and worsen the course of bipolar illness.[6] In fact, childhood trauma has been shown to associate with various degrees of severity of BD, including earlier age at onset, increased risk of suicide attempts, and substance abuse.[14]

Figure. A summary of the different subtypes of BD.



THE PHARMACOLOGIC TREATMENT OF BD

The management of BD may be summarized into 2 phases, acute treatment and long-term prevention. During the acute treatment phase, patients may present with either mania or depression or mixed episodes. According to the APA guidelines, a combination of an antipsychotic, preferably second-generation antipsychotics or atypical antipsychotics, together with either lithium or valproate may be initiated for patients who have severe acute mania or mixed episodes. However, for patients with mild symptoms, monotherapy of lithium, valproate, or an atypical antipsychotic may be sufficient. Short-term adjunctive therapy with a benzodiazepine may also be added if the patient has a partial response to the previously initiated therapy. However, given the high potential for abuse of benzodiazepines with this population, precautionary measures must always be implemented. Alternatively, carbamazepine or oxcarbazepine may be used in lieu of lithium or valproate; meanwhile, ziprasidone or quetiapine may be substituted for another antipsychotic.[4] The 2016 BAP guidelines suggested using haloperidol, olanzapine, risperidone, or quetiapine as first-line therapy to control short-term acute manic symptoms because they have the highest efficacy.[6] However, valproate and lithium are also alternative options for patients who have not been on long-term treatment of BD. The addition of short-term benzodiazepine to promote sleep for agitated overactive patients may be considered as an adjunctive therapy. For patients who are inadequately controlled with the first-line therapy, a combination of lithium or valproate together with a dopamine antagonist (ie, haloperidol or olanzapine) or a partial agonist (ie, aripiprazole) is recommended. In cases of more refractory illness, clozapine may also be considered.

As for the management of acute depression, the APA recommends either lithium or lamotrigine alone as first-line treatment. However, dual therapy