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Mini Review

Lithium – a Loneliness of an Efficacious Unpatented Drug

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Abstract

Lithium is the gold standard drug for maintenance treatment of bipolar disorder. It reduces the recurrence of manic and depressive episodes and decreases the risk of suicide. However, due to its narrow therapeutic index and the fact that its long-term use is associated with several side effects, many clinicians avoid prescribing lithium even to patients who may greatly benefit from its unique therapeutic advantages. In many occasions lithium is sidestepped for fear of side effects, particularly chronic kidney disease. The fact that lithium is an unpatented drug lacking the promotional support of a drug company adds to its relatively lessened glamour.

Keywords: Bipolar disorder; Lithium; Nephrotoxicity; Suicide; Therapeutic efficacy

Abbreviations

BPD: Bipolar Disorder; CKD: Chronic Kidney Disease

Introduction

Bipolar Disorder (BPD) is a disabling psychiatric disorder upsetting 1-1.5% of the general population [1]. It is characterized by alternating episodes of mania and depression and other symptoms, which profoundly disturb the mental, social and functional status of the patients and their relatives [2-4]. BPD is associated with increased incidence of comorbidity with a wide range of medical problems [3,5]. Moreover, suicidal attempts and suicidal death are major factors that contribute to morbidity and mortality among bipolar patients [6].

The pharmacotherapy of BPD consists of various medications but mainly mood-stabilizers and antipsychotic drugs. Several parameters are usually taken into account when deciding on the choice of administrating particular drugs to individual patients (e.g., severity of symptoms, phase/stage of illness, age, gender, family history, medical condition and comorbidities, past responsiveness to medications, among others) [2,4,7-9]. Mood-stabilizers and antipsychotic drugs are given both during acute episodes of the disease and for preventing recurrence of mood symptoms (maintenance therapy). In some cases, other drugs such as benzodiazepines and antidepressants are added during acute manic and depressive phases of the disease to help stabilize the patient [2,4,7].

Lithium is regarded as the corner-stone of maintenance treatment of BPD [2,4,7]. It has a proven effectiveness against recurrence of manic and depressive episodes [2,4,7-12]. The therapeutic efficacy of lithium seems to be higher when the drug is commenced at early stages of the disease [8,13,14], particularly after first episode of mania [9]. The evidence regarding the ability of lithium to decrease the occurrence of depressive bouts is not indisputable. However, recent data suggest that lithium exerts potent prophylactic antidepressant effects [15]. Consistently, lithium reduces the recurrence of depressive episodes also in patients with unipolar depression [16]. Furthermore, lithium has an established ability to decrease suicidal attempts and suicidal death in patients with unipolar depression [16] and BPD [17-19]. There are other therapeutic benefits that were attributed to lithium [20-25] but some of them are still controversial [26-29].

The precise therapeutic mechanism(s) of action of lithium remain(s) unknown. Since its introduction as a useful mood stabilizer, several hypotheses have been proposed to explain its therapeutic efficacy [30-31]. However, none of these is universally accepted [34-39]. A discussion on the mechanism of action of lithium is beyond the scope of this article.

Notwithstanding its established therapeutic efficacy, three factors impede a wider use of lithium: i) it has a plethora of side effects which lead to low adherence and `discontinuation of the drug in some patients; ii) it has a narrow therapeutic index which imposes close monitoring of its plasma concentrations. Plasma concentrations of lithium that are regarded as effective and relatively safe are between 0.6 to 1.2 mEq/liter [4,40]; and, iii) the fact that lithium is an "orphan" drug lacking the promotional support of the pharmaceutical industry. Because lithium is a cheap, naturally occurring chemical, no drug company will invest in its promotion as a useful mood stabilizer. Thus, unfortunately, some clinicians subside or avoid prescribing lithium even in patients who may greatly benefit from its consumption.

Lithium therapy is associated with many side effects [4,40-43]. Possible adverse effects of lithium include gastrointestinal disturbances; neurological problems (e.g., tremor, sedation, weakness, dizziness, memory problems and lack of motivation); cardiovascular alterations (peripheral edema, cardiac arrhythmias and changes in electrocardiogram), skin reactions and aggravation of skin diseases such as acne and psoriasis; endocrine problems (e.g., altered corticosteroids levels and abnormalities in thyroid and parathyroid function); benign leukocytosis; and, most worrying is impairment of kidney function and development of chronic kidney disease (CKD). The severity of side effects may vary between patients, depending on lithium plasma concentration and patients' specific proneness to tolerate the drug. Although the proliferative effect on white blood cells is regarded as an adverse effect of lithium,

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nevertheless, it was suggested as a possible therapeutic strategy for patients with leukopenia [44,45]. Another aspect of lithium toxicity is its potential teratogenic effect. The use of lithium during the first trimester of pregnancy has been linked to an increased risk of congenital malformations [40,46], however, subsequent studies questioned this association [41]. Therefore, this concern should not necessarily discourage the use of lithium in pregnant bipolar women, especially those who were already on lithium before conception and are affectively stable (euthymic). This is because lithium has a prominent therapeutic benefit and an established anti-suicidal effect, and also, the fact that other mood stabilizers also have teratogenic effects (particularly valproate, the use of which in pregnant women is associated with an increased incidence of neural tube defects in the newborns [47,48]).

As mentioned, the most troublesome side effect of lithium is the development of CKD. In this regard, a large body of data suggests that long-term use of lithium increases the risk of CKD [40,42,43,49-52]. However, some studies did not find a causative association between lithium treatment and CKD [41,53]. The response to lithium and severity of its side effects are affected by several factors: patient's characteristics (age, gender, duration of illness, etc.) [41-43]; treatment regimen and plasma concentration [41-43], adherence to treatment [2,10]; genetic background [54]; among others. Many studies suggested that administration of low to medium doses of lithium may reduce the incidence of CKD and, thus, that it is important to administer the lowest effective dose of lithium in order to decrease the incidence of side effects and enhance adherence to treatment [32,43,51,55,56]. Several preventive measures can be followed to decrease the risk of CKD among bipolar patients who take lithium for long durations [43,57].

The prophylactic effectiveness of lithium against recurrence of mood swings [2,4,7-12] and its anti-suicidal effect [16-19] makes it a preferable choice among many clinicians, patients and their families [10,12,43,57]. However, some clinicians avoid using lithium to minimize the risk of nephrotoxicity. It is important to emphasize that other medications that are used for the treatment of BPD also have side effects, some of which are no less harmful than those of lithium [10,12,58]. Another important consideration that has to be taken into account is the high cost of newer anti-bipolar drugs such as second generation antipsychotics [59]. Therefore, in order to utilize the favorable effects of lithium, it is important to search for new strategies to reduce its toxicity – CKD in particular – without conceding its therapeutic benefits.

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