Review



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*Review*

# What Patients with Bipolar Disorder Need to Know about Lithium

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**Abstract:** Lithium is the superior first-line treatment for bipolar disorder (BD). Yet the percentage of patients receiving lithium is abysmally low, especially in the USA. Since psychiatrists have failed to place lithium in its appropriate role, we make the case that patients with BD themselves need to be better educated about the unique characteristics and preeminence of the drug so that it can be used more often and appropriately. Lithium has a highly unfavorable popular reputation among would-be patients and many psychiatrists. Thus, a direct appeal to patients with BD appears appropriate to try to remediate this situation. The unique assets of lithium are underappreciated or not well known. Conversely, the side effects profile of lithium are overestimated. Here, we make the case that lithium's image needs to be revised not only with better and more accurate information but with a wholesale re-naming and rebranding of the drug. We will not only outline the unique qualities and new information about the side effects of the drug but attempt to change some of the terminology conventionally used to refer to lithium so that its use may be appropriately applied earlier and at an increased frequency for patients with BD.

**Keywords:** lithium; bipolar disorder; disease-modifying drug

## 1. Introduction

Lithium is the acknowledged superior first-line treatment for bipolar disorder. Yet the percentage of patients receiving lithium is abysmally low, especially in the United States [1,2]. Elsewhere, we have argued that lithium should be considered an essential disease-modifying drug (DMD) [3], and as such, it should be used earlier and more often to reduce disability and dysfunction.

Lithium is unparalleled in its ability to prevent episodes of mania and depression [4,5]. It also has the best data for preventing suicides. It is most effective when initiated early in the course of bipolar disorder, and when used in this fashion has a major ameliorative effect on the series of adversities that are directly linked to the experience of increasing numbers of episodes [6]. These include an increased frequency and more rapid rate of recurrences; greater severity of recurrences; and episodes requiring fewer precipitating stressors. The underutilization of lithium is particularly problematic in the United States (US) where there is a higher incidence of childhood onset bipolar disorder [7–9] and greater illness severity as manifested by more anxiety disorder and substance abuse comorbidities and more episodes, rapid cycling, and treatment resistance than in the Netherlands and Germany [10]. This appears related to an increase in the incidence of genetic vulnerability in parents and grandparents and an increase in childhood stressors in the US compared to Europe. Lithium is less frequently used in the US than in Europe and this could be additionally contributing to the more adverse course of illness. The long-term follow-up data of Geller et al [11] and Hafemen et al [12] suggest that the use of lithium in youth with bipolar disorder is associated with a better outcome than with other agents and there is less depression and suicidal ideation when lithium is used compared with anticonvulsants and atypical antipsychotics.

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**2. The Unique Assets of Lithium**

Therefore, lithium not only prevents episodes, but it prevents all of the indices of illness progression or what has been referred to as sensitization-like effects or the tendency of the illness to worsen as a function of the number of recurrences [13,14]. As such, lithium should be given the unique designation as a disease-modifying drug (DMD). In the case of medical illnesses such as multiple sclerosis (MS) [15] and rheumatoid arthritis (RA) [16], when disease-modifying drugs are used early in the course of these illnesses, they prevent the associated anatomical progression and functional deterioration accompanying these illnesses. Patients with these illnesses understand that delaying appropriate treatment with DMD drugs places them on a trajectory of irredeemable anatomical abnormalities and functional deficits.

Parents with bipolar illness need to know that their children are at high risk for bipolar disorder and its related comorbidities such as ADHD, anxiety disorders, oppositional defiant disorder, and substance abuse [10,17]. Yet childhood onset illness is poorly recognized and treated. In addition to the diagnosis of early onset bipolar disorder, the delay to first treatment is an independent predictor of more depression and a poor outcome in adulthood [18]. As such, parents with bipolar illness can assist clinicians and physicians in the identification and progression of impairing symptoms in their children. An Institutional Review Board-approved system is available for parents to each week rate the severity of anxiety, depression, ADHD, oppositional behavior, and mania in their child so that the ratings can be printed out and shown to physicians in order to more systematically view illness course and response to treatment [19]. This system can be accessed at www.bipolarnews.org (click on Child Network).

Lack of and delayed use of lithium should be viewed from much the same perspective as that in MS or RA. Many of the deficits associated with multiple recurrences are not readily reversible or reversible at all. This is the case when one considers the many other fundamental assets of lithium in addressing the mechanism underlying the pathophysiology of the illness and illness progression. These deserve to be briefly enumerated here.

Lithium increases grey and white matter volume in the brain and it is unique in increasing the volume of the hippocampus. It does this by increasing several neuroprotective factors BDNF and Bcl-2 and inhibiting cell death factors such as BAX and P-53 [20]. Thus, describing lithium in popular literature as toxic is a complete mis-nomer. It possesses the opposite characteristics: it increases neurogenesis; it reduces all-cause mortality and extends longevity [21]. These are not trivial outcomes, as patients with bipolar disorder normally lose more than a decade of life expectancy, primarily based on increases in cardiovascular events, such as strokes and heart attacks [22]. Lithium also has the strongest data for preventing suicides which occur at a higher rate in bipolar disorder than in any other psychiatric illness [23].

Lithium increases the length of the end strands of DNA called telomeres, which shorten with depression, stress, and aging and are associated with increases in physical and psychiatric illnesses and comorbidities. Lithium activates the enzyme telomerase which places more DNA on the ends of telomeres [24], and does so in proportion to the duration of time a patient is treated with lithium [25].

Lithium also helps resolve some of the fundamental abnormalities associated with bipolar disorder, such as altered circadian rhythms. In addition, it has immunomodulatory effects and even anti-inflammatory and anti-viral effects [26].

While lithium has these unique properties, it is a too common misconception that if treatment with lithium leads to long-term remission, it is possible to slowly taper the drug and discontinue it. The data indicate that stopping lithium in the face of a good long term response does not lessen the risk of a high incidence of relapse, about 50% within 5 months off the drug [27]. In a very small percentage of patients, there is an additional risk of not responding as well as they did before (or even at all) when treatment with lithium is re-instituted [28]. The first author has known about a dozen patients who have experienced this grievous outcome and they all wanted others to know that stopping a treatment that has been working well in the long term, is not without considerable risk including a relapse, a suicide, or inducing an illness that has progressed to the next stage of lithium non-responsiveness and even refractoriness to treatment with multiple other agents as well.

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### 3. Lithium's Adverse Effects Have Been Generally Exaggerated

One of the most widely touted side effects of lithium has been its causing kidney damage that can lead to the necessity of dialysis. Recent data indicate that this idea was largely based on early and uncontrolled observations as bipolar illness itself is associated with renal dysfunction. Two very large nationwide studies in Denmark and Israel have revealed that patients treated with lithium are no more likely to develop end-stage renal failure than those treated with anticonvulsants such as valproate or lamotrigine [29]. These data lead to the conclusion that lithium may be no more toxic to the kidneys than the treatment of bipolar illness with anticonvulsants. Moreover, recent changes in the way lithium is administered, further decrease the likelihood of renal damage This includes; giving lithium in once-nightly doses, attempting to keep levels in the lower end (0.6-0.8meq/L) of the therapeutic range (0.6 to 1.1meq/L); and avoidance of episodes of lithium toxicity.

A more common side effect of lithium on the kidneys is lithium's ability to block the effects of the antidiuretic hormone vasopressin resulting in increases in urination called diabetes insipidus (DI). If urine amounts become problematic, DI can usually be well managed with the addition of the diuretic amiloride which markedly cuts the urine volume and frequency [30].

One often sees the potentially alarming statement that lithium is toxic to the thyroid. This pejorative and misleading characterization distorts the explanation that lithium can interfere with the production of thyroid hormones T3 and T4 and induce hypothyroidism in some 15 to 20% of patients. However, this deficit in hormone production can readily be alleviated with the replacement of thyroid hormone T4 [30].

Another common side effect of lithium is tremor, but in most cases, this can be avoided by lowering the dose of lithium. If this is not effective, the administration of propranolol at doses of 20-80 mg/day is a potentially effective strategy [30]. In cases where the patient is highly sensitive to lithium tremors, and an adequate dose cannot be achieved, lithium can be supplemented with the dihydropyridine calcium channel blocker nimodipine which has lithium-like effects without its tremor or other side effects [31,32]. Nimodipine specifically blocks the calcium influx gene CACNA1C that has been repeatedly linked to an increase in vulnerability to bipolar disorder and depression.

Weight gain is often erroneously touted as an invariable and problematic side effect of lithium. However, recent large long-term follow-up studies suggest that on average this is not the case [33].

Another widely held belief is that lithium impairs cognition or creativity. On the contrary, there is considerable evidence that over one year compared to placebo lithium in low doses prevents cognitive decline in those with mild cognitive impairment [34] and bipolar patients who use lithium have a lower incidence of dementia in old age than nonusers [35].

There are a variety of other less common potential side effects of lithium, but most can be dealt with by appropriate adjuncts or alternatives.

### 4. Questions that Patients with Bipolar Disorder can Ask Their Physicians (Especially if They Are Not Already Being Treated with Lithium)

1) Why am I not on the best medicine for treating and preventing bipolar illness progression?

2) I have had one manic episode; is it not time to use lithium to head off further episodes and their long-term adverse consequences, including more rapid, severe, and untriggered relapses; cognitive dysfunction; disability; and ultimately treatment nonresponsiveness?

3) I am on these other medications but still having episodes. Is it not time to add in lithium as it enhances the effectiveness of most other agents?

4) If you are not well versed in the management of patients on lithium, can you refer me for a second opinion to an expert who is that I can see periodically?

5) Bipolar illness is largely a progressive illness, is it not time that I used the best preventative medicine for it?

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## 5. Some Counterintuitive Statements about Lithium

1) Lithium is not a toxic drug in its usual doses. It is neuroprotective and reparative [26,36]. It increases the amount of grey matter and white matter in the brain, increases the volume of the hippocampus, and increases longevity.

2) Since lithium likely qualifies as a disease-modifying drug (DMD), its use should be mandated earlier and more frequently in preventing the progression of bipolar illness [37].

3) Bipolar illness is one of the psychiatric illnesses with the highest suicide rate, but lithium has the best data for preventing suicide [23]. There are also 10 studies indicating that micro-doses of lithium in drinking water are associated with lower rates of suicide in the general population [38].

4) Lithium is an essential vitamin/mineral. Without its presence, normal growth and development does not occur.

5) Contrary to the even lower utilization of lithium in bipolar disorder in children compared to adults, lithium is highly effective in childhood mania [39], and in long term follow-up studies children on lithium have better outcomes including less depression and suicide [11,12].

6) Lithium in low doses prevents deterioration of mild cognitive impairment [34], and in therapeutic doses reduces the incidence of dementia in old age [35].

7) There is almost no reason not to consider the use of lithium in patients with bipolar disorder.

## 6. Conclusions

Patients with multiple sclerosis and rheumatoid arthritis who do not use disease-modifying drugs (DMD) early in the course of illness know they risk incurring irreversible anatomical and functional deficits. In parallel, patients with bipolar illness who do not use the DMD lithium, risk incurring irreversible anatomical and functional deficits, including cognitive dysfunction, disability, dementia, and premature loss of life expectancy.

Bipolar disorder as it is conventionally treated in the United States is associated with a poor prognosis. Reversing the unwarranted neglect of lithium therapy in a very large segment of the patient population has the chance of making bipolar disorder a much less pernicious illness.

The 75$^{th}$ anniversary of the introduction of lithium should be an occasion for the reassessment of the appropriate role of this drug in the treatment of bipolar disorder and reversing the many decades of its underutilization [40].

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