An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms

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Abstract: Lithium has been used for the treatment of bipolar disorder (BD) for the last sixty or more years, and recent studies with more reliable designs and updated guidelines have recommended lithium to be the treatment of choice for acute manic, mixed and depressive episodes of BD, along with long-term prophylaxis. Lithium’s specific mechanism of action in mood regulation is progressively being clarified, such as the direct inhibition on glycogen synthase kinase 3β, and its various effects on neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, second messenger systems, and biological systems are also being revealed. Furthermore, lithium has been proposed to exert its treatment effects through mechanisms associated with neuronal plasticity. In this review, we have overviewed the clinical aspects of lithium use for BD, and have focused on the neuroprotective and neurotrophic effects of lithium.

Keywords: lithium; bipolar disorder; therapeutic mechanism

1. Introduction

Certainly an oldie, lithium was first pharmacologically used in the nineteenth century, known to have a prophylactic effect on recurrent depression [1]. After the anti-manic effects of lithium were discovered, lithium has been used for the treatment of bipolar disorder (BD), in both the acute and maintenance phases of depression and mania for the last sixty or more years [2]. In the process, prescribing rates of lithium had declined at one point [3] due to the growing doubt on lithium’s evidence-based efficacy as earlier studies on lithium did not meet the more recent research standards [4], along with concerns on the possible fatal toxicity and difficulty of use [5]. Furthermore, the changes in BD diagnostic criteria throughout the years [6], and the appearance of newer agents such as valproate and atypical antipsychotics, may also have influenced the use of lithium [7]. However recent studies with designs considered to be more reliable, such as double-blind randomized controlled trials and meta-analyses, and based on contemporary diagnostic criteria such as Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), have reported lithium to be once again effective in the treatment of BD [8]. Lithium is now considered the treatment of choice for long-term prophylaxis of new episodes [9], regarded as the only substance that prevents both new depressive and new manic episodes [2]. Also, lithium is the only drug with an established anti-suicidal efficacy in BD [10]. Despite such robust treatment effects of lithium, lithium’s specific mechanism of action in mood regulation is still yet to be clarified. Along with the direct inhibition on glycogen synthase kinase 3β (GSK3β), lithium’s various effects on neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, neuronal structures and glia, second messenger systems, and biological systems such as the circadian rhythm and hypothalamic–pituitary–adrenal (HPA) axis, have all been suggested to underlie lithium’s therapeutic effects [11]. Although the pathophysiology of BD has not been completely
elucidated, a large body of literature indicates BD to be associated with significant neuroanatomical alterations [12]. Such results of studies implicate, a compromised integrity of frontal–subcortical and prefrontal–limbic brain regions, in the pathophysiology of BD [13]. Further evidence suggests changes in the cellular level, including dysregulation of glial–neuronal interactions, to underlie such neuroanatomical alterations [14]. Therefore, lithium has been proposed to exert its treatment effects through mechanisms associated with neuronal plasticity [15]. In this review, we will overview the clinical aspects of lithium use for BD, and focus on the neuroprotective and neurotrophic mechanisms of action of lithium. Furthermore, we have mainly included literature emphasizing modern research designs, and have concentrated on the efficacy of lithium as monotherapy rather than in combination with other agents.

Methods

We performed an extensive review of the major publications on the clinical aspects of lithium use, lithium’s treatment effects in BD, lithium’s therapeutic mechanism of action, and neuroimaging studies associated with lithium treatment in BD. A comprehensive literature search of peer-reviewed publications was conducted using PubMed, and relevant articles were identified using the following keywords: “lithium” and “bipolar disorder” and “clinical use’, “lithium” and “bipolar disorder” and “treatment effects’, “lithium” and “therapeutic mechanism’, and “lithium” and “bipolar disorder” and “neuroimaging” and ‘brain structure’. Relevant findings were then identified and synthesized in combination with earlier and extant literature, and referenced articles were further examined to additionally acquire relevant publications. Language was restricted to English, but no time restriction was applied.

2. Guidelines to Initiating and Maintaining Lithium

It is well known that before initiating lithium treatment, a number of essential factors should be considered. First, as lithium is excreted by the kidneys, renal functions must be checked, as decreased kidney functions will lead to excess accumulation of lithium and ultimately toxicity [16]. Renal function test should then be maintained every 6 months during treatment, especially the levels of urea and creatinine [17]. Second, thyroid function tests should be administered as lithium has influence on thyroid stimulating hormone, thyroxine, and triiodothyronine [18]. As a result, the prevalence of both overt and subclinical hypothyroidism has been shown to be increased, with circulating thyroid auto-antibodies frequently being found, and thyrotoxicosis also developing [19]. The prevalence of overt hypothyroidism has been reported to vary from 8% to 19% [20], with the main risk factor being female [21]. Thyroid function tests are recommended to be administered at 6 months, and then annually [17]. Third, serum calcium levels should be checked as lithium is known to cause hyperparathyroidism. The prevalence of hyperparathyroidism is estimated to be 7.5% higher than the general population, and has been reported in patients treated with lithium for 15 or more years [22]. Serum calcium level tests should be conducted at 6 months and then repeated annually [17]. Fourth, lithium treatment is often associated with weight gain, with significant weight gain being observed in patients receiving long term treatment [23]. Also, greater weight gain was observed in patients who were already overweight [24]. Weight, along with waist circumference and body mass index should be checked at 6 months and then annually [17]. Furthermore, electrocardiograms may also be recommended as long-term lithium treatment has been associated with corrected QT (QTc) interval prolongation [25]. Recommended medical examinations for safety monitoring with lithium treatment are listed in Table 1.

In addition to the side effects mentioned above which can occur even when within therapeutic lithium levels, such as reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain [26], typical signs and symptoms of lithium intoxication should also be carefully monitored. Lithium plasma levels greater than 1.2 mmol/L are potentially toxic, and in acute intoxication, plasma levels that exceed 2.0 mmol/L can be fatal [27]. Lithium intoxication is
mainly presented as central nervous system, gastrointestinal, renal, and cardiovascular symptoms. Central nervous system symptoms include a state of confusion, cerebellar signs such as tremor, dysarthria, ataxia, and nystagmus, extrapyramidal and neuromuscular signs such as fasciculations, fibrillations, and myoclonia, and polyneuropathy. Gastrointestinal symptoms include nausea, vomiting and diarrhea, and renal symptoms include polyuria, polydipsia and nephrogenic diabetes insipidus. Cardiovascular signs include arrhythmia, low blood pressure and rarely shock. Adult respiratory distress syndrome or thermoregulation disturbances may also occur [19]. Signs and symptoms of lithium intoxication are summarized in Table 2.

### Table 1. Recommended medical examinations for safety monitoring with lithium treatment.

| Recommended Medical Examination                      | Time of Examination                      |
|-----------------------------------------------------|-----------------------------------------|
| Renal function test                                 | Baseline, every 6 months                |
| Thyroid function test                               | Baseline, at 6 months, annually         |
| Calcium                                             | Baseline, at 6 months, annually         |
| Weight, waist circumference, body mass index        | Baseline, at 6 months, annually         |
| Electrocardiogram                                    | **Electrocardiogram recommended for the risk of QTc interval prolongation** |

### Table 2. Signs and symptoms of lithium intoxication.

| Symptoms                                      | Lithium Intoxication > 1.2 mmol/L                          |
|-----------------------------------------------|-----------------------------------------------------------|
| **Central nervous system**                    | State of confusion                                        |
|                                               | Cerebellar signs (tremor, dysarthria, ataxia, nystagmus)  |
|                                               | Extrapyramidal and neuromuscular signs (fasciculations, fibrillations, myoclonia) |
|                                               | Polyneuropathy                                             |
| **Gastrointestinal**                          | Nausea, vomiting, diarrhea                                |
| **Renal**                                     | Polyuria, polydipsia, nephrogenic diabetes insipidus.     |
| **Cardiovascular**                            | Arrhythmia, low blood pressure, shock.                    |
| **Adult respiratory distress syndrome**       | Thermoregulation disturbances                             |

Although the half-life of lithium in the brain is approximately 24 h, the half-life in plasma is 8 h [28]. A single daily dose of lithium may also be an acceptable option [29,30], but a majority of therapeutic guidelines recommend divided daily doses of lithium, in order to maintain a steady plasma level [31,32]. Two or more daily doses may be applied initially to achieve a standardized 12-h serum lithium level [33], followed by a full daily dose which will aid to enhance compliance and decrease the chance of increased urinary volume [34]. A therapeutic lithium plasma level for BD has been recommended as 0.5–1.2 mmol/L [31], and when initiating treatment, lithium levels should be checked at a steady state, which is at least five days after taking a certain dose, until two consecutive levels within the therapeutic range are established for the same dosage [17]. Lithium has a relatively narrow therapeutic index, and individual differences should be accounted for when initiating treatment as lithium toxicity may occur if levels surpass 1.2 mmol/L. Therefore, lower plasma therapeutic levels at initiation of treatment, such as 0.6–0.8 mmol/L have also been recommended, which can be increased to 0.8–1.0 mmol/L when recurrence occurs [35]. As maintenance therapy, a therapeutic level of 0.4–0.6 mmol/L [31] and up to 0.6–0.8 mmol/L [32] have been recommended. However, it is suggested that plasma level titration is needed according to polarity and symptomatic profile [36], and different prophylactic levels have been recommended for depression-prone BD patients and mania-prone patients, with the levels being 0.4–0.8 mmol/L and 0.6–1.0 mmol/L respectively [37].

Of note, two forms of acquired nonresponse to lithium that develop over the treatment course in patients who have previously shown adequate response have been reported. The first type of nonresponse is discontinuation-induced refractoriness, is when patients who have showed good long-term response to lithium then discontinue treatment, and after experiencing a major recurrence, do not respond to lithium at previously effective doses [38]. The second type of nonresponse is the
development of a pharmacodynamic tolerance to lithium, described as mild, brief, or infrequent symptoms starting to occur then progressively increasing in severity, duration, or frequency, until the original pattern of illness prior to treatment recurs, even while maintaining lithium treatment [39]. Physicians should be aware of the possibility of occurrence of the two phenomena while maintaining treatment in patients with BD, and apply appropriate management of the conditions when necessary.

3. Lithium in the Treatment and Prophylaxis of Bipolar Disorder (BD)

Lithium has been reported by recent literature to be effective in treating manic and mixed episodes compared to placebo, including numerous randomized controlled trials (RCTs) [40–42] and meta-analyses [43–45]. When compared to other mood stabilizers and atypical antipsychotics, lithium was shown to have similar treatment efficacies in acute manic and mixed episodes as valproate [46,47], olanzapine [48], risperidone and haloperidol [49]. On the other hand, manic or mixed patients taking lithium were shown to have less response but no significantly different remission rates compared to patients taking olanzapine [50]. Also, manic but not mixed or rapid cycling patients taking lithium were reported to show less response and a lower remission rate compared to those who were on quetiapine [51]. Lithium was also suggested to be more effective in manic patients compared to valproate [52] and olanzapine [53]. One RCT reported an equal efficacy of verapamil compared with lithium in the treatment of mania [54]. Studies of adequate quality comparing the efficacy of lithium with other anticonvulsants and mood stabilizers such as oxcarbazepine, lurasidone, gabapentin and tiagabine, have not yet been conducted [8]. Furthermore, no RCTs have yet investigated the treatment effects of lithium in purely mixed or hypomanic patients, with a systematic review suggesting lithium monotherapy to lack significant prophylactic benefits in mixed episodes [55]. Concerning onset of action, lithium has been reported to have a slower onset of action compared to antipsychotics such as haloperidol, olanzapine and risperidone, with lithium being 6–10 days [56] and antipsychotics being 2–6 days [57].

Although only a few RCTs have been conducted on the treatment effects of lithium in bipolar depression, several treatment guidelines recommend lithium as a first-line treatment agent for bipolar I disorder (BD-I) depression [58]. Possibly considered a disadvantage, lithium has been shown to have less efficacy in treating bipolar depression compared to quetiapine and antidepressants such as venlafaxine by previous studies. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in the acute phase of BD-I or bipolar II disorder (BD-II) major depression reported quetiapine, but not lithium, to have significant treatment efficacy compared to placebo [59]. A subsequent open-label, randomized study on the treatment effects of quetiapine or lithium monotherapy in patients with BD-I or II major depression reported both agents to reduce depressive symptoms, but the remission rate to be higher with quetiapine [60]. A randomized, parallel group, open-label trial on venlafaxine and lithium monotherapy in rapid and non-rapid cycling patients with BD-II depression reported venlafaxine to have superior efficacy compared to lithium independent of cycling status, and to not result in a higher proportion of mood conversions [61]. On the other hand, lithium has shown equal efficacy compared to other medications such as lamotrigine, as a single blind study of lithium and lamotrigine treatment for BD-II depression reported both agents to be effective with similar response and remission rates [62]. Furthermore, considered as advantages of lithium therapy, a protective effect against switching to mania when treating bipolar depression [63], and a reduction in the risk of suicidal behavior which is often accompanied in bipolar depression [64], have been suggested with lithium treatment. However, the antidepressant effect of lithium has been reported to have a delayed onset of 6–8 weeks. Therefore, in clinical practice, a combination of lithium with other agents which are considered to be effective in the treatment of bipolar depression, is more likely to be administered, and despite the insufficient evidence, lithium remains important in the treatment of bipolar depression [65].

Lithium has been shown to be effective in the prophylaxis of both mania and bipolar depression [66], hence the majority of treatment guidelines recommend lithium as a first-line agent for
maintenance therapy. A RCT including patients with BD-I and a current or recent manic, depressive, or mixed episode reported lithium to significantly increase time to recurrence of both manic events and depressive events compared with placebo [67]. A randomized open-label trial including patients with BD-I and were not having an acute episode but were indicated for long-term therapy, reported lithium monotherapy to be more likely to prevent relapse than valproate monotherapy [66]. Based on previous evidence, lithium has been suggested to provide better prophylactic efficacy against manic episodes compared to depressive episodes [8].

As BD is often presented with psychotic features especially during manic episodes, the efficacy of lithium treatment on bipolar psychosis has previously been investigated [68]. However, only a few studies have systematically evaluated lithium’s treatment effects on mania with psychosis. Studies comparing lithium with first and second-generation neuroleptics in mania with psychosis reported chlorpromazine to be superior than lithium in treating psychotic features [69], and aripiprazole but not lithium, to be more effective than placebo in treating psychotic symptoms [40]. On the other hand, lithium was shown to have similar efficacy as quetiapine, and to be superior to placebo in the treatment of psychosis in manic episodes [41]. Furthermore, lithium monotherapy was shown to be significantly better than placebo in improving mania in a psychotic subtype [70], to produce early improvement of psychotic symptoms, and to have similar efficacy in both psychosis and non-psychosis mania [71]. Future research on lithium’s anti-psychotic properties in the treatment of BD should be conducted.

The anti-suicidal effects of lithium in BD have previously been reported by numerous RCTs and meta-analyses. A meta-analysis published in 2006 which included 31 studies and 33,340 subjects, reported risks of completed and attempted suicide to be lower during lithium treatment in patients with BD and major depression [72]. In a meta-analysis published in 2009, which included 6 studies that directly compared patients with BD who were treated with either lithium or anticonvulsants (carbamazepine, divalproex, lamotrigine), reported suicidal acts to be significantly lower during treatment with lithium [73]. A meta-analysis published in 2013 which included 48 RCTs, also reported lithium to be more effective than placebo in reducing the number of suicides in patients with mood disorders, although no clear benefits were observed for lithium in preventing deliberate self-harm [64]. Not only considered a consequence of lithium’s mood stabilizing effects, the anti-suicidal effects of lithium have also been associated with the reduction of impulsivity and aggressiveness, both of which are associated with an increased risk of suicide [74], and are often present in bipolar depression or mixed states [75]. Furthermore, lithium’s numerous mechanisms of action, including the inhibition of GSK3β, have been suggested to contribute to lithium’s anti-suicidal properties [76]. The therapeutic mechanisms of lithium are discussed in detail in the below section.

4. Therapeutic Mechanisms of Lithium

Although the specific therapeutic mechanisms of lithium in mood regulation has not been clarified, lithium is recently being suggested to exert its mood stabilizing effects by acting on cellular targets and exerting neuroprotective effects [77]. The GSK-3 signaling pathway modulates apoptosis and synaptic plasticity, with increased activity supporting apoptosis, and attenuated activity enhancing neuroplasticity and cellular resilience [78]. Manipulation of the GSK-3 pathway has been shown to produce both antimanic and antidepressant effects [79], and genes regulating GSK-3 have been implicated in BD etiology [80,81]. Lithium is considered to influence numerous neuroprotective pathways through increasing phosphorylated GSK3β and inhibiting its action, ameliorating the effects of excitotoxicity [82]. Previous studies have reported treatment response to lithium to be predicted by GSK3β gene expression and phosphorylation [83,84], and lithium induced increases in phosphorylated GSK3β to be correlated with symptom improvement [82]. Brain-derived neurotrophic factor (BDNF) is well known for its involvement in neuronal maturation, differentiation and survival, synaptic plasticity, and long-term memory consolidation, and is highly expressed in the cerebral cortex and hippocampus [85]. Numerous studies have reported decreased BDNF levels in patients with bipolar
depression and mania, along with low levels of BDNF to be correlated with severity of depression and mania symptoms [86,87]. BDNF gene polymorphisms have also been associated with the risk for BD, early onset of the disease, suicidality, propensity toward rapid cycling, and treatment response [88,89]. Lithium has been suggested to prevent cellular degeneration through BDNF upregulation, with chronic lithium treatment shown to increase BDNF [90].

Mitochondrial function is known to be essential for regulating neuroplasticity, apoptosis, and intracellular calcium levels. Changes in endocellular calcium have an essential role in modulating intracellular signaling cascades and neurotransmitter release [91]. Defective mitochondrial function has been associated with abnormal oxidative metabolism and damage to deoxyribonucleic acid (DNA), which contributes to neuronal apoptosis [92,93]. Mitochondrial dysfunction has been implicated in BD, with hippocampal expression of genes related to mitochondrial proteins being reduced in patients with BD [93]. Furthermore, accelerated telomere shortening observed in BD, has been suggested to be greatly influenced by stress-related oxidative damage [94]. Lithium has been shown to have anti-oxidative effects through various mechanisms such as increasing the antioxidants [95], reducing the expression of stress proteins [96], reducing proinflammatory molecules and attenuating immune responses to stress [97–100], and influencing the expression of genes involved in oxidative cytoprotection [101]. Studies conducted on patients with BD have reported lithium to decrease lipid peroxidation levels [102], and ameliorate mitochondrial dysfunction, which reverses the effects of oxidative stress [103]. Previous studies have reported lithium to prevent apoptosis by modulating GSK3β [104], tumor protein p53 [105] and B-cell lymphoma 2 [106], to increase neurons, glial cells and astrocyte density in brain areas such as the hippocampus [107], stimulate re-myelination and repair demyelinated pathways [108]. Furthermore, various other second messenger systems are thought to be involved with the therapeutic effects of lithium, including the phosphoinositide cycle, protein kinase C, and intracellular Ca²⁺ [109]. Lithium is considered to ameliorate inositol depletion-related mitochondrial dysfunction by inhibiting inositol monophosphatase 1 [110], to enhance reparative neuronal plasticity by inhibiting protein kinase C through a myristoylated alanine-rich C kinase substrate pathway [111], to maintain Ca²⁺ homeostasis by downregulating the transient receptor potential channel 3 [112], and to enhance cyclic adenosine monophosphate (cAMP)-induced cAMP response element-binding protein (CREB) dependent gene transcription [113].

Disturbances in various neurotransmitter systems have been reported in BD. Numerous studies including meta-analyses have suggested glutamatergic dysregulation to underlie the pathophysiology of BD, with elevated levels of glutamate-related metabolites being observed in prefrontal–limbic brain areas [114], and such glutamatergic dysregulation suggested to reflect glial abnormalities [115]. Also, the expression of subunits of NMDA glutamate receptors in the hippocampus, has been shown to be decreased in BD [116]. Dopaminergic dysfunction has also been implicated in BD, with excessive dopaminergic activity in mania precipitating dopamine receptor down-regulation, and inducing a transition to depression [117]. Previous studies have also reported abnormalities in gamma-aminobutyric acid (GABA) transmission in BD, with alterations in GABA platelet uptake [118] and GABA transmission [119], along with increases in GABA/creatinine ratio [120]. Lithium has been shown to modulate such neurotransmitters including glutamate, dopamine, GABA, acetylcholine and glycine [109]. For glutamate, lithium has been reported to act on presynaptic terminals and inhibit excitatory postsynaptic currents [121], increase enhancers and promoters of genes associated with glutamate neurotransmission [122], decrease phosphorylation of N-methyl-D-aspartate (NMDA) receptor subunits post-synaptically [123], along with NMDA-induced cytoskeletal deterioration [124]. In patients with BD, lithium has been shown to have a bimodal action in hippocampal glutamate concentration depending on the plasma levels [125]. For dopamine, lithium is considered to exert a regulatory effect and has been shown to prevent excessive dopamine release [126]. For GABA, lithium has been reported to influence its neurotransmission, but the effects being less, compared to glutamate [121]. For acetylcholine and glycine, lithium was recently reported to have influence on
both neurotransmitters, by attenuating depressive behaviors through cholinergic pathways [127], and differentiating the expression of glycine transporters on neural cell surfaces [128].

There has been an increase in findings on lithium’s effects on circadian rhythms and the HPA axis, which are both considered to be associated with the pathophysiology of BD. A significant amount of evidence indicate an association between circadian dysregulation and BD. Alterations in sleep structure such as increased REM sleep density, sleep pattern variability, sleep latency, sleep duration, number of arousals, and fragmented sleep, along with decreased sleep efficiency have been implicated in BD [129,130]. Alterations in endocrine and neurotransmitter diurnal rhythms have also been suggested in BD, with changes in melatonin secretion [131] and diurnal glucocorticoid regulation being reported. Associations between circadian genes such as TIMELESS, ARNTL1, PER3, NR1D1, CLOCK, and GSK3β, and BD have also been suggested [130]. Lithium has been shown to resynchronize circadian rhythms [132] by modulating clock gene expression [133], and the treatment effects of lithium have been shown to be mediated by circadian components [134]. Alterations in HPA axis function in BD include excess corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) secretion, which ultimately increase cortisol levels [135]. Furthermore, decreased sensitivity of glucocorticoid receptors which leads to the disruption of the HPA axis feedback regulation, has also been implicated in BD [136]. Lithium has been suggested to activate the HPA axis, as lithium’s influence on protein kinase C can in turn influence the expression of corticotrophins in the adrenal glands [137].

5. Lithium and Brain Structure

The majority of changes in the cellular level, neurotransmitter and neurotrophic systems [138,139] indicate alterations in neuroplasticity to underlie the pathophysiology of BD. In order to elucidate the neuroanatomical phenotype of BD, numerous imaging studies have been conducted, although the results have been frequently equivocal and non-replicable. However, certain brain regions have constantly been implicated in BD. Increased lateral ventricle volume that correlates with number of episodes, has been identified in patients with BD, which indicates BD to be progressively deleterious to the brain [140,141]. The ventromedial prefrontal cortex (PFC) is connected to limbic structures, and is involved in processing emotionally relevant information. Decreases in volume of the ventromedial PFC have been shown in adolescent patients with BD, but equivocal findings have been reported in adult patients [142]. The dorsolateral PFC, which is part of an executive–cognitive network that regulates limbic structures, has been shown to be decreased in thickness in patients with BD [143]. The anterior cingulate cortex (ACC) connects prefrontal cortical areas with subcortical limbic regions, and plays an important role in cognitive–emotional integration. Volume reductions in the ACC have been reported in patients with BD. Inconsistent findings regarding hippocampal volume exist, with increased, decreased and no difference in volume being observed in patients with BD [144]. As amygdala volume has been reported to differ according to age group in BD, with smaller volumes being observed in adolescent patients, and larger volumes being observed in adult patients, it is suggested that structural changes of the amygdala may reflect progression of the disease [145]. Alterations of volume of other subcortical regions, including the nucleus accumbens, putamen and caudate have also been reported, but with mixed results [142]. Alterations in white matter (WM) integrity have also been widely reported by numerous diffusion tensor imaging studies in patients with BD. WM tracts connecting the ACC with the amygdala and hippocampus, and the frontal lobe with the insula, amygdala, hippocampus, occipital lobe, thalamus and cingulate gyrus, have all been observed [146,147]. Such compromised integrity of frontal–subcortical and prefrontal–limbic brain regions, may support an organic basis for the symptomatology of BD.

In order to investigate the putative neurotrophic and neuroprotective effects of lithium, numerous imaging studies have been conducted for the last decade. Although previous studies have also reported no effect of lithium on brain structure [148–150], numerous studies have reported positive effects of lithium on gray matter (GM) volume and WM integrity. BD patients who were treated with lithium showed significantly greater GM density compared to healthy controls in diffuse
cortical regions, particularly in the cingulate and paralimbic cortices, with the neurotrophic effects of lithium suggested as a possible etiology of such neuroanatomic differences [151]. Lithium was also shown to attenuate the decrease in both GM and WM in BD patients [152]. Daily dosage of lithium treatment was positively correlated with superior temporal gyrus volume in patients with BD [153], and BD patients on lithium also showed increased GM in the subgenual anterior cingulate gyrus, postcentral gyrus, hippocampus/amygdala complex and insula compared to patients on other treatment agents [154]. Significantly decreased thalamus volume in lithium-free BD patients was reported compared to healthy controls, whereas lithium-treated BD patients showed no difference to the healthy control group [155]. In patients with BD depression, long-term lithium treatment was associated with increased GM volumes including the dorsolateral PFC, orbitofrontal cortex, ACC, superior temporal cortex, parieto-occipital cortex, and basal ganglia [15]. BD patients with over two years of lithium treatment showed hippocampal volumes comparable to controls, whereas patients with limited lifetime lithium exposure showed significantly lower hippocampal volumes compared to controls [156], with the findings being replicated in a subsequent study [157]. Imaging genetics studies have been conducted on the influence of lithium and GSK3β promoter rs334558 polymorphism on brain structure in patients with BD. The less active GSK3β rs334558*C gene-promoter variant and long-term administration of lithium, were associated with increased WM integrity in regions including the corpus callosum, forceps major, cingulum, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, posterior thalamic radiation, superior and posterior corona radiata, and corticospinal tract [158]. Lithium treatment and the GSK3β promoter rs334558 polymorphism was also synergistically associated with increased GM volumes including the subgenual and orbitofrontal cortex in patients with BD depression [159]. A recent meta-analysis on GM volume in BD patients with and without lithium treatment reported global GM volume to be significantly larger in lithium-treated BD patients compared to lithium-free patients [160]. However, due to the lack of correlations between alterations in certain GM and WM structures and improvement of BD symptoms, brain structural changes associated with lithium treatment may not always be interpreted as direct results of the therapeutic effects of lithium, and the findings from imaging studies should be interpreted with caution.

6. Conclusions

BD is a heterogeneous condition with a myriad of symptoms varying in manifestation, and the dysregulation of numerous biochemical pathways have been suggested to be involved in the pathogenesis of BD. As the complex therapeutic mechanisms of lithium are gradually becoming unraveled, it is becoming more evident that the cellular mechanisms and biological systems modulated by lithium, are deeply intertwined with the biological disruptions implicated in BD. Therefore, a deeper and clearer understanding of the specific therapeutic mechanisms of lithium, will aid us to establish a better understanding of the complex mechanisms underlying the pathophysiology of BD. Although it is undeniable that lithium is effective in the treatment and prophylaxis of BD, certain subtypes of the disorder seem to respond less to lithium, and not all patients benefit from its treatment effects. The identification of biologic predictors of lithium response remains an important step in the pursuit of personalized medicine for the treatment of BD [161]. As current neuroimaging techniques enable us to study the underlying neurobiological mechanisms of BD, along with the neuroprotective and neurotrophic effects of lithium, future imaging studies are anticipated to facilitate the identification and investigation of biologic predictors of lithium response. The fact that lithium has withstood several ordeals, such as the concerns on its possible fatal toxicity and difficulty of use, and has stayed strong as the treatment of choice for BD for over six decades, proves lithium to be a goodie. Even Nirvana made a song about it.

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