REVIEW: SHOULD LITHIUM REMAIN AS THE GOLD STANDARD AND FIRST-LINE TREATMENT FOR PATIENTS WITH BIPOLAR DISORDER?

Authors: Wan Ezzeriq Bin Wan Zalik¹ and Rafidah Bahari*  
Affiliation: Faculty of Medicine, University of Cyberjaya, Persiaran Bestari, Cyber 11, 63000 Cyberjaya, Selangor, MALAYSIA.  
Corresponding author: Rafidah Bahari (rafidahbahari@cyberjaya.edu.my)

Abstract

Most guidelines around the world recommends lithium as the first line medication in the treatment of bipolar disorder. Lithium has numerous side effects, and with the introduction of newer mood stabiliser and antipsychotics which are also efficacious, should this recommendation remain? In the light of newer published evidence, the role of lithium as the gold standard and first line treatment of bipolar disorder is reviewed.

Keywords:

Living in the epoch of nanotechnology, the stigma surrounding mental health issue remains strong. Even in the year 2021, public stigma towards psychiatric patients has shown to be detrimental. In a qualitative study done by Hanafiah & Van Bortel (2015), they discovered that stigma towards psychiatric patients in Malaysia is now higher than it had been a decade ago, with many still trapped in the vicious cycle of discrimination. They further elaborate that a joint effort between the public and government must be made in order to successfully challenge this negative perception held tightly by the general population. The government must do what it can to educate the public. On the other hand, healthcare professionals must manage psychiatric illnesses. The correct diagnosis and management are imperative to improve patients’ quality of life and be beneficial members of society. Despite its narrow therapeutic index, lithium still is regarded as the gold standard in most hospital policies and international guidelines (Malhi, 2013). However, on what basis is such a recommendation?

BD is characterised in the Diagnostic and Statistical Manual V (DSM-V) by episodic recurrences of mania or hypomania episodes and depressive episodes with or without psychotic features at the duration that markedly varies in between individuals. Over decades, researchers have proposed an extensive variety of theories, but the pathophysiology of BD remains poorly understood. Rosenblat and McIntyre (2017) proposed that bipolar disorder has a strong connection with the immune dysfunction where many of the suggested mechanisms have been strongly proven in animal models. They postulated that, cytokines are able to directly alter the monoamine levels, which subsequently causes microglial cells to be over-activated. Prior to this alteration, there were also increase in the brain oxidative stress giving rise to neurodegeneration and deteriorating brain neuroplasticity. This in turn leads to the phenotypic changes that can be observed during cerebral imaging of BD patients. This mechanism is called the inflammatory-mood pathway, proving the ability of circulating peripheral cytokines to cross the blood brain barrier which subsequently alters the brain structure. Another theory is the adrenergic-cholinergic balance hypothesis that was first introduced in 1974. Van Enkhuizen, (2015) revisited the theory and hypothesised that a catecholaminergic-cholinergic balance hypothesis is way more relevant compared to the immune dysfunction theory.
Evidence from neuroimaging studies, clinical trials and genetic research have now proven that both theories are, to an extent, correct. When the cholinergic function is enhanced, it is a cardinal key in depressive episodes. However, enhancement in the catecholamines functioning e.g. dopamine and norepinephrine, plays a key role during the manic episodes (Van Enkhuizen, 2015).

How does this pathophysiology explain the mechanism of action of lithium carbonate? While there is a growing body of literature, the mechanism of action of lithium remains unclear. Malhi (2013) proposes that lithium works in two different mechanisms at the neuronal level; the promotion of gamma-Aminobutyric acid (GABA) neurotransmission, and secondly, the inhibition of dopamine (catecholamine) neurotransmission. As mentioned, the sole aim of the first mechanism is to increase GABAA level in the cerebrospinal fluid (CSF) and therefore raising thus the inhibitory effects. With the assistance of the lithium, the enhancement of GABA receptors at the presynaptic neurons facilitates the GABA release into CSF whilst at the postsynaptic neurons, lithium is responsible for the upregulation of GABA receptors. GABA is an inhibitory neurotransmitter that plays a major role in the modulation of dopamine and glutamate neurotransmission, which is strongly thought to be fundamental in the stabilisation of mood which is central in the treatment of BD.

Aside from facilitating GABA release into the system, lithium is also responsible for the inhibition of dopamine neurotransmission. In the mechanism of dysregulation of dopamine, the aforementioned effects of dopamine during mania could be halted. Lithium exerts its inhibitory effects at receptors, targeting three different locations i.e. dopamine receptor (DA) itself, inactivation of post-synaptic G-proteins coupled receptors and downregulation of N-methyl-D-aspartate (NMDA) receptors. Once adenylyl cyclase (AC) and myo-inositol (ml) systems are downregulated, there will be a modulation of dopamine neurotransmission hence reducing the severity of the mood symptoms (Malhi, 2013).

Having established the pathophysiology of BD and the mechanism of lithium at the neuronal level, what is it about lithium that makes it the gold standard treatment of BD? A group of French researchers carried out a bioanalysis study to further explore lithium’s pharmacokinetics and pharmacodynamics. In the study, they confirmed that the clinical use of lithium could be precariously tricky due to its narrow therapeutic index (Couffignal et al, 2016). This is supported by Wen et al (2019) who established that lithium is rapidly and directly absorbed from the gastrointestinal tract after its oral administration, making it difficult to determine the dosage for each patient. The trouble lies in this careful balance, where a relatively minor surge in the lithium serum level may give rise to serious adverse effects, while inadequate amounts is ineffective (Couffignal et al, 2016). Over the years, researchers have been attempting to yield new chemical entities that might possess better bioactivities with a safer therapeutic window (Smith, 2014). According to Wen (2019), lithium level is initially highest in the serum before it is redistributed to the various tissue compartments. Furthermore, lithium is not metabolised and over 95% of lithium salt is excreted unchanged through urine. Having said that, some novel lithium salts may overcome these issues in the future, but further study on their pharmacokinetics are needed to establish the optimal formulation, dosage and best route of administration.

In 1949, when lithium carbonate was first introduced by John Cade as a treatment for manic excitement in psychiatric patients, people were skeptical about its benefits and extent of ability to treat mania. Even today, the unpleasant origin of its ominous beginning has not entirely resolved (Baldessarini, 2020). However, studies supporting its efficacy helped to gain lithium’s acceptance. In a randomised controlled trial (RCT) done in 2018, lithium showed better efficacy than quetiapine in maintaining remission (Severus et al, 2018). In a series of studies comparing the rate of psychiatric hospitalisation and rehospitalisation in BD patients shows consistent findings. In their studies, some patients were prescribed with lithium and other patients with other mood stabilisers such as risperidone, gabapentin, lamotrigine and carbamazepine. They observed a marked reduction of psychiatric hospitalisation in BD patients with lithium prescription and the use of lithium was also
found to have the lowest risk of association with any cause of hospitalisation compared to any other compounds used (Lähteenvuo et al, 2018). For instance, Lähteenvuo and team further described that even the most widely used agent, quetiapine proved to have a modest effectivity with only 8% of risk reduction of psychiatric hospitalisation.

Sani et al (2017) carried out another study to validate the efficacy of lithium in managing BD patients. Their conclusions were in line with previous research. In addition, they also compared the long-term use of antipsychotics and mood stabilisers with their polarity index (PI). PI refers to the relative antimanic versus antidepressive efficacy value i.e. a value of greater than 1.0 (> 1.0) indicates anti-manic efficiency, while a value below than 1.0 (<1.0) indicating antidepressant properties. They concluded that lithium displays a better prophylactic efficacy in mania, hypomania and mixed episodes through reducing the risk of relapse (Sani et al, 2017). Furthermore, in patients with a successful course of maintenance phase, it is not recommended for them to stop taking lithium since almost one third of them relapses in the first year when they do so (Sani et al, 2017). Hence, the evidence for lithium use as the first line medication is robust.

Nevertheless, is its use justifiable despite the potential harm? According to Ganti et al (2016), toxic levels of lithium may adversely affect multiple organ systems, ranging from the nervous, gastrointestinal and endocrine system, and even teratogenicity. Shah et al (2015) reported that damage to the nervous system occurs even at high dose maintenance therapy. However, some of this neuronal damage is reversible (Netto and Phane, 2012). Apart from being neurotoxic, lithium is also known to possess nephrotoxic features. The most common known renal side effects secondary to lithium consumption is nephrogenic diabetes insipidus (NDI). It is a condition where nephrons are unable to respond towards vasopressin or antidiuretic hormone (ADH). It is suggested that lithium can directly cause the destruction of renal cells, particularly the collecting duct cells, hence desensitizing it towards vasopressin (Behl et al, 2015). An alternate theory proposed is that lithium inactivates the AC messenger and reduces the levels of cyclic adenosine monophosphate (cAMP), which unequivocally disrupts the regulation of urine. When the AC-cAMP pathways is inhibited, there will be a downregulation of the phosphorylation or expression of aquaporin-2 (AQP-2), consequentially leading to the incapability of collecting duct cells to concentrate the urine, resulting in lithium-induced NDI (Behl, T. et al., 2015; Dastych, M. et al., 2019). In addition, lithium also causes hypothyroidism. Various theories on how lithium affects the normal physiology of thyroid gland have been proposed, but alteration of iodine reuptake at thyroid gland is said to be the cornerstone of lithium-induced hypothyroidism (Kibirige, D. et al., 2013). Other researchers proposed that due to the inhibition of the cAMP pathways, lithium disrupts the hypothalamic-pituitary-thyroid (HPT) axis which allows the genesis of thyroid hormones production (Ahmad et al, 2013). This is in line with the study by Kibirige where they discover that apart from being densely accumulated at the hypothalamus, lithium itself may halted the activity of deiodinase enzymes responsible for deiodination of tetraiodothyronine or thyroxine (T4) to activate triiodothyronine (T3) (Kibirige et al, 2013). Nevertheless, this seems to be an effect following longstanding administration of lithium, especially in high doses.

It is also accepted that gravid mothers who are taking lithium may be predisposed to de trop incidence of Ebstein's anomaly in newborns. Ironically, while this is accepted by most clinician, it has been debated between researchers since the evidence to associate lithium and Ebstein's anomaly is scarce. In a cohort study by Poels et al (2018) found that lithium can directly affect gravid mothers under lithium therapy due to its ability to freely cross the blood placental barrier. However, in another study looking at cases across Europe, they concluded that the association between lithium and Ebstein's anomaly is extremely weak, with the prevalence being only about 0.47 cases in 10, 000 births in Europe from 1982 to 2011 (Boyle et al, 2016). They suggested that the incidence of Ebstein’s anomaly is closely related to maternal general health condition rather than the consumption of lithium.
per se. Hence, it can be concluded that although one study confirms Lithium’s role in the aetiology of Ebstein’s anomaly, larger scale study has failed to find a strong association. Nevertheless, it is recommended that BD patients on lithium therapy must be closely monitoring during the antenatal period in the slight chance that it may cause Ebstein’s anomaly.

Most importantly, even though lithium may cause all these harms, its use may in fact reduce one major harm. Many studies have found out that one Lithium’s notable and unique property is its ability to reduce suicidal risk of patients with BD. In one comparative study in between lithium versus placebo and lithium versus anticonvulsants such as lamotrigine, they discovered that lithium causes a significant reduction of suicidal behaviours compared to others. They added that lithium seems to be more efficacious in preventing suicidal attempts in patients with depressive BD and even patients with major depressive disorder (MDD) (Tondo & Baldessarini, 2018). Another meta-analysis uncovered that with a long-term treatment of lithium, the reduction of death by suicide is approximately 20% and suicide attempts is around 10% (Benard, 2016). They further elaborate that because of lithium’s specific action on the 5-Hydroxytryptamine (5-HT) serotoninergic receptors, this has given rise to its anti-suicidal effects via the modulation of impulsiveness and aggressiveness in patients with BD and MDD. Furthermore, according to Miller and Black (2020), even when suicide is difficult to predict, early intervention with lithium may offer robust advantages in lowering patients’ risk of suicidal behaviours. In addition, they also stated that long-term use of lithium may reduce the risk of death for approximately 60-80% in all patients with BD (Miller & Black, 2020).

Hence, despite the introduction of newer mood stabilisers, lithium remains the gold standard medication for BD. As highlighted, due to its antimanic and antidepressive properties, it is highly recommended as the first line of treatment especially in BD patients with predominantly depressive mood. In addition to that, even with its detrimental side effects, we are fully capable of monitoring patients and treat them safely on the lithium regime. Last but not least, prior to its uniqueness in ability to reduce the suicidality behaviours in patients with depressive symptoms, lithium remains as the gold standard treatment for BD. For patients with recurrent suicidal thoughts and attempts, then it is hypothesised that long-term use of lithium might help in the prevention of suicidality. As the famous phrase goes “an ounce of prevention is worth a pound of cure”.

References


www.turkjphysiotherrehabil.org

4875


32. Tondo, L., & Baldessarini, R. J. (2018). Antisuicidal effects in mood disorders: are they unique to lithium?. *Pharmacopsychiatry, 51*(05), 177-188.


