**Lithium: old and new observations**

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1. **INTRODUCTION**

Lithium's modern history traces back to 1949, when Australian psychiatrist John Cade utilized it to treat patients with mania and observed notable enhancements [1]. Lithium was approved as a medication in multiple countries: France in 1961, the United Kingdom in 1966, Germany in 1967, Italy and the USA in 1970. Lithium, a soft, silvery-white alkali metal with atomic number 3, has been found in small quantities in animal tissues. In contrast to sodium and potassium, it creates a rather limited distribution gradient through biological membranes. While it can mimic sodium to trigger a nerve cell's action potential, it is not a suitable substitute for the sodium pump and therefore cannot raise the membrane potential.

Presently, there are immediate-release and prolonged-release lithium formulations accessible for human consumption.

Despite being over 60 years old, lithium remains the top choice for preventing manic and depressive episodes in bipolar disorder [2]. Lithium is suggested for: augmentation of antidepressants, treating severe depression, managing aggressive behavior, and preventing suicide; it should only be considered for cluster headache if other treatments have been ineffective. This medication is also used for Kleyne-Levine syndrome, psychogenic polydipsia, and as a combination strategy in treating patients with treatment-resistant schizophrenia [1]. Lithium's therapeutic effects are a result of its immunomodulatory, antiviral, and neuroprotective properties [3]

1. **GENETICS**

The patients exhibit different behaviors when treated with lithium salts. Around 20 to 30% of patients experience lasting improvement in their condition [4], either partially or completely (lithium responders), while 30% are considered partial responders and 40% show no improvement at all [4]. Other factors are also at play, as genetics can only account for a limited portion of this diversity [5]. Individuals who show a full recovery with lithium treatment tend to have family members who also exhibit a full recovery and similar disease pattern. Genes eligible to be linked to lithium response [4] include those encoding GSK-3β, BDNF, and the serotonin transporter. Patients who possess beneficial genetic variants in the chromosome 21 region experience a much lower relapse rate compared to patients without these variants [4].

1. **Pharmacokinetics**

Lithium is available in tablet form for oral consumption. It is effectively taken in by the gastrointestinal system with an oral bioavailability ranging from 80-100% [1]. Lithium does not bind to plasma proteins; its distribution volume is approximately 0.7 – 1.0 L/kg; hepatic cytochromes do not metabolize it, and it is excreted as a free ion in the kidney [1]. The plasma half-life is about 24 hours; the stable phase occurs between days five and eight. 90% of it is eliminated through urine. Immediate-release formulations are quickly taken in, reaching peak serum concentrations in 1-2 hours after being taken orally, whereas prolonged-release formulations take 4-5 hours to reach their peak values [1].

Lithium can pass through both the blood-brain barrier and the blood-cerebrospinal fluid barrier [1]. Plasma levels should range from 0.4 to 1.0 mEq/L. The target lithium serum level is 0.60 to 0.80 mmol/L, with the option to adjust to 0.40 to 0.60 mmol/L for good response but poor tolerance, or 0.80 to 1.00 mmol/L for insufficient response but good tolerance (ISBD/IGSLI) [1]. Toxic manifestations can arise when levels are between 1.5-2.5 mEq/L, becoming lethal if surpassing 3.5 mEq/L [1].

Medications that either decrease or increase the renal excretion of lithium are the most important drug interactions with lithium in clinical practice. [1]

1. **Pharmacodynamic**

It is now known that lithium has an impact on several processes in cellular communication.

Animal studies showed an increase in serotonergic transmission, including synthesis of serotonin, tryptophan uptake, and serotonin release [2].

After being administered acutely, it enhances the release of glutamate, hinders glutamate reuptake, and activates NMDA receptors by outcompeting magnesium ions. After a few days, this process is reversed, with lithium decreasing levels of glutamate at synapses by enhancing its reuptake [2].

Lithium treatment appears to have no effect on basal dopamine levels but does block heightened dopamine activity, potentially by affecting β-arrestin complexes [2].

One of the primary ways lithium affects the body's biochemical processes is by blocking glycogen synthase kinase-3β (GSK-3β), leading to changes in intracellular signaling, particularly within the phosphatidylinositol system. GSK-3β is known for its role in regulating various biological processes such as gene expression, embryonic development, neuronal survival, synaptic plasticity, apoptosis, cellular structure, resilience, and circadian rhythms, all of which are involved in the development of mood disorders [6].

Lithium blocks inositol monophosphatase-1 and protein kinase C (PKC), and impacts adenyl cyclases that transform ATP to cyclic adenosine monophosphate (cAMP). CREB, primary element of this system, regulates gene expression through cAMP response [6].

Furthermore, lithium affects the brain-derived neurotrophic factor (BDNF), crucial for neuron survival and function, explaining its mood-stabilizing effects and potential neuroprotective properties [6]. Extended use of lithium was discovered to enhance levels of brain-derived neurotrophic factor (BDNF) in intracellular and extracellular of cortical and hippocampal nerve cells. Inhibition of GSK3β directly might lead to an increase in BDNF expression [2].

The reason for the decrease in suicidal thoughts and behavior is not fully understood; various mechanisms may play a role, including effects on serotonin receptors or increased glutamate release and activation of the GABA system [1].

Pharmacodynamic drug interactions between lithium, selective serotonin reuptake inhibitors, and first generation antipsychotics are uncommon occurrences [1]. Certain drugs can raise the amount of lithium in the bloodstream.

1. **SIDE EFFECTS**

Nephrogenic diabetes insipidus and lithium nephropathy are the primary adverse effects associated with lithium [1]. Lithium can cause kidney-related side effects such polyuria, nephrogenic diabetes insipidus, protein in the urine, distal renal tubular acidosis, and decreased glomerular filtration rate [7]. Chronic damage to the kidneys caused by lithium is identified, histologically, interstitial nephritis with microcyst formation and occasional focal segmental glomerulosclerosis [7].

Goiter and hypothyroidism are the most common negative outcomes related to the thyroid [8]. Women and individuals with a family history of thyroid issues are more likely to experience symptoms of hypothyroidism during the beginning of lithium treatment [8].

Among other potential side effects of lithium, weight gain and tremors, which may arise at the onset of lithium treatment, should be noted [8].

1. **LITHIUM DURING PREGNANCY**

It is very difficult to manage Bipolar Disorder during pregnancy due to the potential risks of using mood stabilizers or not receiving any treatment, as these risks have not been fully assessed or measured. This leads to decisions about treatment that rely on risks that are not fully understood [9; 10; 11; 12; 13; 14 ; 15; 16; 17; 18; 19; 20; 21; 22].

Lithium is a freely crossing ion that passes through the placental barrier [23]. Birth defects, especially heart-related ones, have been linked to the use of lithium in the first trimester of pregnancy. Information from a database of children who were exposed to lithium while in the womb revealed a 400-fold rise in heart defects, specifically Ebstein's anomaly [24], in the exposed children compared to those who were not exposed [25].

The incidence of Ebstein's anomaly in the general population is 1 in 20,000. It is characterized by downward displacement of the tricuspid valve [24], right ventricular dysfunction, and tricuspid regurgitation [26]. In their research, Cohen and colleagues [27] investigated studies on lithium exposure in pregnancy and discovered that the rate of cardiovascular defects while using lithium in the first trimester was 0.05-0.1%, significantly higher than the general population, but lower than previously thought [13].

Diav-Citrin and colleagues [28] conducted a comparison between pregnancies exposed to lithium and those not exposed to lithium, finding potential congenital abnormalities in both groups. The rate of cardiovascular abnormalities was greater in the group exposed to lithium [28], however, when excluding resolved abnormalities, this difference was not significant from a statistical standpoint.

Patorno and colleagues analyzed 1,325,563 pregnancies, with 663 involving lithium exposure and 1945 involving lamotrigine exposure; they gathered information from the Medicaid registry in the United States for the study [29]. The relationship between lithium exposure and heart defects, such as Ebstein's anomaly, depended on the dose [29]. The adjusted hazard ratio was found to be 1.65 higher when compared to controls and 2.25 higher when compared to those exposed to lamotrigine, in terms of cardiac malformations [29]. The estimated risk of heart defects was found to be about one extra occurrence for every 100 babies born alive [29]. No link was identified between lithium exposure and noncardiac malformations by any research organization [29].

However, in a study analyzing 727 pregnancies where lithium was used and 21,397 pregnancies without lithium with matching diseases, it was found that the risk of major malformations, including heart defects, was greater in pregnancies with lithium exposure (OR 1.62, 95% CI 1.12- 2.33) in mothers with mood disorders compared to those without exposure. The study did not show a significant rise in the risk of heart defects [30]. While the evidence is not definitive, it is advised to have conversations about continuing lithium treatment with female patients with bipolar disorder before and during pregnancy. For instance, it could be beneficial to decrease lithium in the initial stage of pregnancy, but the possibility of a recurrence should be taken into account. If lithium is still being taken, a “fetal cardiac ultrasound should be done at 20 weeks of gestational age but could be suggested earlier, at 16 weeks” [31].

The exact cause of congenital birth defects in fetuses exposed to lithium is still unknown: could it be the effect of lithium on glycogen synthase kinase-3β (GSK3β)? [34] This enzyme is crucial for the Wnt signaling pathway [33], which plays a role in the development of the heart and blood vessels in embryos [31; 32].

Lithium clearance by the mother's body varies during pregnancy, gradually rising from 30% to 50% in the latter half. The clearance decreases abruptly after birth but goes back to pre-pregnancy levels [35]. Higher amounts of lithium may be required during pregnancy to offset the increased elimination rates, potentially leading to toxicity. It is generally advised to stop taking lithium towards the end of pregnancy to lower the chance of lithium poisoning in the mother from build-up, and to start taking it again in a small amount after giving birth to prevent a relapse of manic and/or depressive symptoms [31].

Limited information is available regarding the progression of Bipolar Disorder during pregnancy, and the likelihood of relapse is not accurately measured. During pregnancy, the uncertainty regarding the risk of relapse is still present, despite it being well-defined in the postpartum period.

Salim's recent review concluded that many women with BD are prone to relapses during pregnancy, with depressive episodes being the most common [36]. Studies examined reported a greater rate of recurrence in individuals who stopped taking mood stabilizers [36] [37; 38; 39; 10].

When it comes to the postpartum period, studies show that around 40% to 55% of women with bipolar disorder and a history of recurrent episodes are at risk of experiencing at least one episode within the first six months after giving birth [40].

A recent meta-analysis combining data from multiple sources shows that around "37% of women with BD experience symptoms during the postpartum period" [41]. The likelihood of experiencing mania and/or psychosis is significantly elevated in women with BD right after giving birth [42]; in fact, these women are 37 times more prone to psychiatric hospitalization than during any other period in their lives [43]. Specifically, women with bipolar I disorder (BD I) and schizoaffective disorder-bipolar type (SA-BD) are especially at risk [43].

Guidelines differ on the optimal treatment approach for pregnant women. Therefore, it is advisable to take into account the NICE guidelines (NICE 2014) [44] that suggest thinking about stopping lithium during the initial trimester and transitioning to a different antipsychotic. Regarding lithium treatment, it is important to inform the woman about the dangers of birth defects.

Alternatively, Australian and New Zealand recommendations [45] argue that lithium is the preferred medication for reducing relapses, with antipsychotics as a possible substitute.

**A. What to do in case of pregnancy?**

According to information from the literature, here are some practical guidelines to adhere to for pregnant patients undergoing lithium therapy. [46].

1. Keep the lithium levels in the individual at the lowest protective amount

2. If a pregnant woman is exposed to lithium during the first trimester, potential heart defects can be identified through hight resolution ultrasound examination (level II) and echocardiography screening between weeks 16-18 of pregnancy [47] [48]

3. Regularly check lithium levels: guidelines from NICE and NVVP suggest monitoring every month in the first 7-8 months of pregnancy, and weekly monitoring from 34 weeks until delivery when significant changes in kidney function could affect lithium clearance [41].

4. During pregnancy, there is an increased excretion of lithium through the kidneys, which means higher doses are needed to maintain stable levels of lithium in the blood. [49].

5. Some authors recommend splitting up the daily lithium dose into several doses to prevent the unborn child from being exposed to high peaks [50]

6. Do not use treatments that could raise the chances of lithium toxicity (such as ACE inhibitors, diuretics, NSAIDs, low-sodium diet), unless adjusting the lithium dosage is necessary [38].

7. Decrease lithium dosage if there are issues like preeclampsia or polyhydramnios which can increase the risk of lithium toxicity [38].

8. Stop giving lithium to pregnant women 24-48 hours before a planned cesarean delivery or induced delivery, or at the onset of labor for a spontaneous delivery [38].

9. If spontaneous delivery occurs, ensure to assess maternal lithium levels upon the patient's arrival at the hospital [38].

10. Make sure to keep hydrated by drinking fluids or receiving fluids through an intravenous during childbirth and monitor lithium levels if signs of toxicity appear [38].

11. Lithium treatment should be resumed post-delivery once the patient is in good medical condition. The pre-pregnancy dosage should be administered when the glomerular filtration rate goes back to its original levels [38].

12. Lithium is excreted in breast milk, therefore mothers should not breastfeed [11].

**VII.Conclusions**

Lithium is considered the gold standard of long-term treatment for bipolar disorder, however, effective patient management and experience are necessary [2], and it is safe when used in specialized clinics [51].

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