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LITHIUM SNUBBED, YET STILL VALUABLE: REVIEW OF ITS CLINICAL USE IN PSYCHIATRY

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ABSTRACT

The availability of several antiepileptic drugs and atypical antipsychotic agents for the management of bipolar disorders has almost rendered the use of lithium salts (hereafter, 'lithium') obsolete in the armamentarium of many 21st century clinicians. The purpose of this review is to summarize lithium's history, its mechanism of action, its interaction with other medications, its dosage, its administration, and the monitoring of its serum blood level. The valuable clinical role of lithium as a mood stabilizer for the treatment of acute bipolar mania, bipolar depression, and for the prevention of mood episodes associated with bipolar disorders is reasserted. Lithium's effectiveness as an augmenting agent in treatment-resistant unipolar major depressive disorder, its role in reducing the risk of suicide in patients with mood disorders and its neuroprotective effects on improving the prognosis of cognitive disorders is also summarized.

KEYWORDS: Lithium, Depression, Mania, Psychopharmacology, Suicide.

INTRODUCTION

Lithium is an effective mood stabilizer,[1] although there continue to be detractors.[2] Along with atypical antipsychotic agents[3] and anticonvulsant/antiepileptic agents, it is still considered one of the most effective clinical options for the treatment and management of bipolar disorders.[4] Lithium can also be used as an effective adjunctive therapy for recurrent treatment resistant major depressive disorder, and it possesses anti-suicidal properties which are of utmost clinical importance in the overall management of mood disorders.[5,6] Relatively lithium is not difficult to use and generally well tolerated in most patients while periodically monitoring its blood levels given its narrow therapeutic /toxic window.[7] Lithium's long term adverse effects, especially those related to the kidney, the thyroid and the parathyroid glands, need to be carefully assessed and frequently monitored.[8] Complications could occur as consequence of lithium interacting with medications that affects its plasma level. Therefore, clinicians should closely monitor these interactions to prevent subtherapeutic or toxic lithium levels.[9] In the current psychiatric practice climate, lithium's risks and potential adverse effects appear to have been exaggerated and could be appropriately minimized with a clearer appreciation of its therapeutic profile and its usefulness perhaps as the only true available mood stabilizer. Despite its proven clinical effectiveness and unique properties, lithium is underutilized and subsequently substantial number of patients are being deprived of the optimum opportunity to mitigate their mental suffering and disability and to optimize their well-being with this arguably remarkably unparalleled and effective therapeutic agent.

Historical background

Lithium derives its name from "lithos," the Greek word for stone, because it is present in trace amounts in virtually all rocks. As early as 200 A.D., Galen recommended bathing in alkaline mineral waters, which might have contained lithium, for the treatment of mania.[10] During the mid-1800s, lithium carbonate solutions were used to treat gout due to its uric acid calculi and crystals dissolving properties, eventually this treatment was found to be ineffective.[11] Lithium was also used in the treatment of epilepsy and cancer.[12] In the 1940s, lithium was widely used as a salt substitute and was also added to some soft drinks.[13] The occurrence of several deaths due to lithium toxicity among patients with hyponatremia lead to the discontinuation of these practices and the development of a popular perception toward lithium as being a dangerous agent for use in clinical settings. In the meantime, psychiatrist, John Cade in Australia, observed and documented lithium calming effects on guinea pigs and wondered if the same calming effects could occur when lithium is administered to patients.

After trying it out on himself to establish safe doses, Dr. Cade began treating some patients with mania, and published an article in the Medical Journal of Australia in which he described the marked mood stabilizing effects of lithium.[14,15] In another development Dr. Mogens Schou, a Danish psychiatrist who had a brother with untreated and detrimental mania, was impressed by Dr. Cade's discovery and cooperated with Dr. Poul Baastrup to conduct a double-blind, placebo-controlled clinical trial, which confirmed lithium effectiveness for the treatment of bipolar disorder, including Dr. Schou's brother.[16] In the 1950s and for the following two decades, lithium became widely accepted as an effective treatment for bipolar disorder. In 1970, lithium was approved by the United States Food and Drug Administration (FDA) for the treatment of mania.[17] In the late 1980s, a gradual decrease in lithium use prevailed in clinical practice which coincided with the approval of some anticonvulsants and atypical antipsychotics as mood stabilizers.[18] In the late twentieth century and early twenty-first century; lithium use declined which was attributed to concerns about its adverse effects, its narrow therapeutic-toxic level, and its potential effects on renal,[19] thyroid[20] and parathyroid functions.[21]

Mechanism of action

The mechanism of action of lithium as a mood stabilizing agent remains illusive, unclear and has been described as complex, and multi-faceted. Recent findings suggest lithium neuroprotective effects to be related to its regulation of the endoplasmic reticulum (ER) stress proteins.[22,23] The ER is the site of synthesis and folding of a large fraction of the total protein output in a cell and the conserved ER stress response is considered vital in maintaining cellular resilience.[24,25] These findings suggest that lithium's therapeutic mechanism involves the maintenance of ER homeostasis through its effects on increasing mesencephalic astrocyte-derived neurotrophic factor (MANF) gene expression which is mediated via the transcription factor activator protein-1 (AP-1).[25]

Pharmacodynamics

Lithium exerts multiple pharmacodynamic effects. It modulates glutamatergic and gamma-aminobutyric acid (GABA) receptors. It alters the excitatory effects of dopamine and adrenaline. It also has modulating effects on serotonin.[26] It also acts through multiple pathways that could alter intracellular signaling via second messenger systems by inhibition of inositol monophosphate. This inhibition, in turn, affects neurotransmission through the phosphatidylinositol secondary messenger system. It also decreases protein kinase C activity,

which alters genomic expression associated with neurotransmission. Lithium appears to increase cytoprotective proteins, possibly activates neurogenesis, and increases gray matter volume by exerting neuroprotective effects of slowing or even preventing neuronal loss.[27] These possible mechanisms of action of lithium are not fully understood and most likely interrelated.

Pharmacokinetics

Lithium has simple pharmacokinetics that require regular dosing and monitoring. Brain lithium nuclear magnetic resonance spectroscopy findings have delineated the post dose brain and blood lithium concentrations, as well as the pharmacokinetic basis for lithium response and nonresponse.[27,28]

Lithium is rapidly and completely absorbed from the gastrointestinal (GI) tract following its oral administration. Its highest level is in the serum, then it is redistributed though the general circulation to body organs. Lithium does not undergo any significant metabolic pathways and over 95% of lithium is excreted unchanged through the kidney.

Absorption: Following its oral administration, lithium is rapidly absorbed and has lower absorption on an empty stomach. It is absorbed in the upper GI tract. The peak serum concentrations (Tmax) occur 0.25 to 3 hours after oral administration of the immediate release preparations and 2 to 6 hours after sustained-release preparations.[29]

Distribution: It is hydrophilic and distributed throughout the body depending on the availability of water. Its distribution approximates that of total body water, with negligible plasma protein binding capacity.[30] Once the equilibrium is established, the apparent volume of distribution is 0.7 to 1 L/kg. Lithium distribution is influenced by lean body mass resulting in an increased of its level in individuals with smaller lean body mass, such as in the elderly. Some magnetic resonance spectroscopy studies have shown that brain lithium levels are highly correlated with plasma levels[31] except in the elderly, who may have higher central nervous system (CNS) levels, showing normal plasma lithium level.

Metabolism: As a natural salt, lithium is not metabolized by the liver and is not significantly protein-bound. Its clearance relies entirely on renal functions and it has no active metabolites.[32]

Excretion: Lithium is primarily excreted in urine in proportion to its serum concentration. It is filtered by the glomerulus with 80% being reabsorbed by passive diffusion in the proximal tubule.[32] Lithium excretion in feces is insignificant. The elimination half-life of lithium is approximately 18 to 36 hours, so steady-state serum levels are typically reached after 5 days.

Lithium interaction with other medications

Lithium clearance is easily influenced by drugs that alter renal function such as the angiotensin-converting enzyme (ACE) inhibitors, diuretics, and non-steroidal anti-inflammatory drugs. It is therefore prudent for prescribers to monitor and adjust the lithium dose under these circumstances to avoid adverse effects or loss of efficacy.[33] Medications, such as the nonsteroidal anti-inflammatory drugs (NSAIDs) or other cyclooxygenase-2 (COX-2) inhibitors, may decrease renal blood flow and increase lithium levels. Diuretics, which act on the distal renal tubules, tend to increase lithium levels. On the other hand, diuretics, that act on the proximal renal tubules, generally have less of an effect on lithium levels. The ACE inhibitors also increase lithium level. Hydration status can affect lithium levels. During stages of hypovolemia or hyponatremia, lithium levels increase. It is important to avoid lithium use in individuals who are on low salt diet to prevent the development of hyponatremia. Metronidazole raises lithium levels by decreasing its renal clearance. Carbamazepine, phenytoin, and methyldopa may increase lithium toxicity. List of various medications effects on lithium are summarized in table1.[9,34]

Table 1: Clinical consequences of lithium interaction with medications.

Medications	Clinical consequences
Diuretics: Chlorothiazide, hydrochlorothiazide, furosemide, etc.	Induction of hyponatremia due to loss of sodium, could decrease lithium clearance and increase serum lithium concentrations and could precipitate lithium toxicity.
Angiotensin-converting enzyme (ACE) inhibitors: Lisinopril, enalapril, captopril, valsartan, etc.	Increased in steady-state serum lithium concentrations.
Calcium channel blocking agents (CCB): Verapamil, diltiazem, nifedipine, etc.	Increased risk of neurologic adverse effects such as ataxia, tremors, nausea, vomiting, diarrhea, tinnitus.
Non-Steroidal Anti-inflammatory drugs (NSAID): Ibuprofen, indomethacin, naproxen, etc.	Decrease renal blood flow, resulting in decreased renal clearance and increased serum lithium concentrations.
Serotonin augmenting agents: Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors	Possible precipitation of serotonin syndrome which could be manifested by agitation or restlessness, insomnia, tachycardia, hypertension. dilated pupils, loss of muscle

(SNRIs), monoamine oxidase inhibitors (MAOIs), etc.	coordination or twitching, muscle rigidity profuse sweating, diarrhea, headache, shivering and goose bumps. In its most severe presentation it could be life-threatening and presenting with high fever, tremors, seizures, irregular heartbeats and loss of consciousness.
Acetazolamide, Urea, Xanthine preparations, Alkalinizing agents: Acetazolamide, theophylline, sodium bicarbonate, etc.	Could increase serum lithium concentrations secondary to reduced renal clearance.
Second generation (Atypical) and first generation (Typical) Antipsychotic medications: Risperidone, clozapine haloperidol, thioridazine, fluphenazine, chlorpromazine, perphenazine, , etc.	Severe neurologic adverse effects including extrapyramidal side effects, neuroleptic malignant syndrome, and encephalopathic syndrome have been documented in some case reports.
Neuromuscular blocking agents (NMBAs): Succinylcholine. rocuronium, doxacurium, etc..	Lithium may prolong the effects of NMBAs.
Central Alpha-2 receptor agonists: Methyldopa	Possible increased risk of methyldopa adverse reactions such as difficulty breathing; swelling face, lips, tongue, or throat.
Antiepileptics (Anticonvulsive) agents: Phenytoin, carbamazepine, etc..	Possible increased risk of adverse reactions of these drugs such as acute confusion, excitement, nystagmus.
Nitroimidazole antibiotics: Metronidazole, tinidazole.	Could increase steady-state serum lithium concentrations.
Iodide preparations: Potassium iodide	Could induce hypothyroidism manifested by fatigue, increase body weight, cold intolerance and infertility.

Lithium medical work-up

Prior to treatment initiation, it is important to obtain a complete physical examination to include checking of vital signs, body weight, serum electrolytes, renal function tests, and thyroid function tests. The presence of any cardiac symptoms or abnormality warrant an electrocardiogram (ECG). Concurrent medications should be assessed for their potential effect on lithium serum level. The risks and benefits of lithium therapy need to be carefully and judicially assessed in childbearing individuals, during the crucial periods of pregnancy, postpartum, and nursing of newborns. Informed consent and educational materials about the use of lithium, its monitoring requirements, its potential adverse effects, its therapeutic and toxic levels, are necessary to assure the safety and ongoing adherence with the recommended dose and daily schedule of this pharmacological intervention.

Contraindications

Lithium is contraindicated in patients with known hypersensitivity to any active or inactive ingredient in any of the lithium formulations. Lithium is also not recommended in patients with preexisting cardiovascular disease since it could causes reversible T wave changes and can unmask Brugada syndrome; an inherited disorder associated with risk of ventricular fibrillation and sudden cardiac death in a structurally normal heart.[35] A cardiology consult is necessary if a patient experiences unexplained palpitations and syncope in the course of lithium therapy. There has been concern that exposure to lithium during the first trimester of pregnancy may be associated with a marked increase in the risk of Ebstein's anomaly, a congenital heart defect characterized by a malformation of the tricuspid valve and right ventricular outflow tract obstruction defect in infants. Recent research studies have confirmed a lower than previously reported lithium induced incidence of Ebstein's anomaly.[36] Tapering and discontinuation of lithium during the first trimester could be considered but should be weighed against the risks of relapse into manic episodes versus the possibility of developing Ebstein's anomaly.

Administration

Lithium is administered orally in pill or capsule form (as its carbonate salt), or in a solution or liquid form (as its citrate salt). Tablets are available, by prescription, in a controlled release 450 mg tablet or in a 300 mg slow-release formulation. Capsules are available, by prescription, in 150 mg, 300 mg, and 600 mg strengths. The liquid formulation is available as 8 mEq/5 mL strength. There is also a formulation of lithium, 'lithium orotate,' that can be obtained over the counter in pill denominations ranging from 5 mgs to 120 mgs. The various types of prescription lithium formulations are summarized in Table 2. The conversion of lithium tablets to oral solution conversion is summarized in Table 3.

Table 2: Lithium's various formulations.

Lithium carbonate capsules 150 mg, 300mg, 600mg	***Lithium carbonate extended*** *Release Tablets* 300mg, 450mg	***Lithium citrate liquid*** 8 milliequivalents (mEq) of lithium per 5 milliliters (mL) of solution

Table 3: Lithium Carbonate and Lithium oral solution dose conversion.

Lithium carbonate tablets	Lithium oral solution
150 mg	4 mEq (2.5 mL)
300 mg	8 mEq (5 mL)
600 mg	16 mEq (10 mL)

Lithium Dosing and Treatment regimen

It usually takes 5 days for lithium to reach its steady state concentration. Thus, lithium levels are usually checked about 5 days after its initiation. Lithium level should always be checked 12 hours after the last dose. The therapeutic effects of lithium and symptoms remission may take up to 3 weeks to be clinically observed. Lithium is usually initiated at the dose of 300 mg two or three times daily. In the elderly, the dose may need to be reduced to 150 mg twice daily. If tolerated well, based on response and body mass index, the dose could be increased by 300 to 600 mg every one to five days. The goal of upward dose adjustment is to reach a therapeutic serum level, which generally occurs with a dose range of 900 mg to 1800 mg per day. Dose increases generally occur more frequently at the beginning of treatment, and less often as the therapeutic dose is reached. A single nighttime dose may be considered to minimize side effects in some patients who have been stable on a particular therapeutic dose. This once a day dosing strategy could improve treatment adherence.

Monitoring lithium levels

The target therapeutic serum lithium level is between 0.8 and 1.2 mEq/L (0.8 and 1.2 mmol/L); the levels should not exceed 1.2 mEq/L (1.2 mmol/L) to prevent the risk of toxicity. Patients who cannot tolerate a level of 0.8 mEq/L (0.8 mmol/L) may respond to a level of 0.6 to 0.7 mEq/L (0.6 to 0.7 mmol/L). Lithium levels should be measured five to seven days after each dose increase. Levels are drawn 12 hours after the last dose and generally collected in the morning, before the first dose of the day. Whenever possible, lithium should be tapered gradually over a span of three months. Abrupt discontinuation of lithium could increase the risk of relapse into acute manic episodes.In addition to regular monitoring of serum lithium level for patients on maintenance treatment, the level should be monitored after any change in dosage and during concurrent treatment with medication listed in Table 1. Any change in daily routines that alter body hydration status, would also warrant checking of lithium level. Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels that are within what is considered a normal therapeutic range. Elderly and medically compromised patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels that are usually tolerated by other patients.

Dosage adjustments for patients with renal impairment

Patients with mild to moderately impaired renal functions, should be treated with lower initial doses and slower upward titration. They need more frequent monitoring of serum lithium

levels as well as vigilant assessment for any signs of lithium toxicity. Most clinical guidelines do not recommend lithium use in patients with severe renal impairment.[37]

Dosage adjustments during Pregnancy and The postpartum period

Lithium use during pregnancy is associated with an increased risk of spontaneous preterm birth and other adverse neonatal outcomes. These potential risks must be balanced against the important benefit of treatment and should be used to guide shared decision-making between patients and their health care providers.[38] If lithium treatment is deemed necessary to be maintained during pregnancy, lithium levels need to be more frequently monitored, and dosage adjustment would need to be implemented due to the effects of pregnancy on increasing renal lithium clearance. Sodium restriction and diuretic administration need also to be avoided. To decrease the risk of postpartum lithium intoxication, decreasing or discontinuing lithium therapy two to three days before the expected delivery date is recommended to reduce neonatal concentrations of lithium and to reduce the risk of maternal lithium intoxication as a result of vascular volume change that occurs during delivery. Restarting treatment at the preconception dose could be initiated once medical stability is achieved after delivery with ongoing monitoring of serum lithium concentrations.

Lithium adverse effects

The most common adverse effects of lithium along with their treatment strategies are illustrated in table 4.[39]

Table 4: Treatment strategies for managing lithium side effects.

Side effects	Treatment strategies
Gastrointestinal side effects such as nausea and diarrhea	Taking lithium after meals, using a multiple daily dose regimen or using sustained release preparations may diminish nausea. Diarrhea occurs more frequently with sustained release lithium preparations Need to rule out lithium toxicity if diarrhea persists.
Polyuria	Once-daily dosing, if clinically feasible.
Polydipsia	The use of sugarless gum, glycerin-based oral moisturizers, lemon drops and mouthwashes could minimize the urge of excessive fluid intake which could precipitate hyponatremia and contribute to lithium toxicity.
Fine hand tremor	Beta-blockers such as propranolol, primidone, pyridoxine (Vitamin B6)
Weight gain	Avoiding high-calorie drinks, high caloric and high fat diets, and implementing daily physical activities and

	exercises.
Sexual dysfunction	In the absence of medical contraindications, initiation of adjunctive treatment with phosphodiesterase 5 inhibitors such sildenafil, vardenafil, and tadalafil, could be recommended to maintain lithium treatment adherence .
Skin lesions (Acne, psoriasis)	Dermatology consult may be warranted.

Tolerance occurs with some side effects such as nausea but not weight gain. Similarly, dose adjustments may be helpful with some but not all side effects. Specific dose/side effect relationships are not well established for a number of side effects. Altering the time of the lithium ingestion should always be considered when managing some but not all side effects. Changing the lithium to a different preparation—from capsules to sustained release or vice versa— could be helpful for the gastrointestinal side effects. Adjunctive use of additional medications to specific side effects should be considered based on their risk/benefit ratio and patients consent. Additionally, the side effects associated with the adjunctive agents must always be considered and thoroughly explored with each patient. Clinicians, who are reluctant to consider lithium treatment, are mostly concerned about its renal, thyroid, and parathyroid long-term adverse effects.

Lithium renal effects

Lithium induced renal disease is characterized by a progressive decline in renal function, evidenced by increasing serum creatinine and decreased creatinine clearance.[37] The lithium salt causes direct injury to the renal tubules. The duration of lithium therapy increases the risk of progression to end-stage renal disease (ESRD), however, discontinuation of medication may not necessarily halt the progression of ESRD. The most serious concern is the possibility of lithium-induced interstitial nephropathy.[40] which can develop after 10–20 years of treatment and leads to increased creatinine concentration, as well as a decreased glomerular filtration rate (GFR). This can even lead to the discontinuation of lithium, a clinical decision that require a careful evaluation, particularly for patients with long good response. In the majority of these patients, discontinuing lithium could result in high risk for relapse and further treatment resistance.[41] Risk factors associated with decreased GFR include, longer duration of treatment, higher serum lithium concentration, older age, presence of co-occurring medical conditions, and the initiation of lithium treatment after the age of 40.[42] The implementation of specific measures, such as once-daily dosing schedule, achieving the lowest effective serum lithium concentration, and preventing lithium intoxication, could offer long term protection of renal functions.[43] In patients with lithium-induced nephropathy,

renal function should be closely and frequently monitored in collaboration with nephrology services. Since the progression of renal dysfunction is slow, if discontinuing lithium is clinically indicated, an alternative mood stabilizer should be initiated and gradually titrated to its therapeutic dose prior to tapering and the discontinuation of lithium which could gradually occur over a 4–8 weeks period.

Thyroid effects

Because of the active transport of Na^+/I^- ions, lithium, despite its concentration gradient, lithium is accumulated in the thyroid gland at a concentration 3 - 4 times higher than that in the plasma.[44] It can inhibit the formation of colloid in thyrocytes, change the structure of thyroglobulin, weaken the iodination of tyrosines, and disrupt their coupling. In addition, it reduces the clearance of free thyroxine in the serum, thereby indirectly reducing the activity of 5-deiodinase type 1 and 2 and reducing the deiodination of these hormones in the liver.[44] Several clinical guidelines recommend the performance of thyroid ultrasound and checking the levels of thyroid hormones (T3 and T4), TSH, antithyroid peroxidase and antithyroglobulin antibodies prior to the initiation of lithium therapy[45]. It is also advisable to perform thyroid ultrasound and to check TSH level at 6- to 12-month intervals in patients with initial normal thyroid functions who receive long term lithium therapy, TSH level measurement and thyroid ultrasound should be performed at 6- to 12-month intervals for long term. The lithium-induced hypothyroidism usually appear at the early stage of lithium treatment and are more frequent in women and in individuals with a family history of thyroid dysfunction.[45] The frequency of goiter in lithium-treated patients seems to be similar in men and women. Hypothyroidism and goiter could be adequately treated with levothyroxine, and the appropriate dose could be determined through an endocrinology consultation.[46]

Parathyroid effects

Lithium may induce hypercalcaemia by increasing renal calcium reabsorption and independently stimulating parathyroid hormone (PTH) release. Symptoms of hypercalcemia include weakness, fatigue, the development of renal stones, renal insufficiency, and osteoporosis. Lithium induction of hypercalcaemia is a consequence of both its acute and chronic effects.[47] The initial acute effects are potentially reversible in contrast to the long term effects of lithium which could lead to permanent changes within the parathyroid similar to primary hyperparathyroidism and resulting in increased morbidity.[48] Although current clinical practice guidelines do not recommend regular monitoring of calcium and PTH levels

with lithium-treated patients, measuring calcium levels both before the initiation of lithium treatment and yearly during treatment is clinically prudent since the early recognition of lithium-associated hyperparathyroidism can improve its prognosis.[48] Asymptomatic patients with mild level elevation of lithium-associated hypercalcemia/ hyperparathyroidism only need to be monitored. With higher calcium levels, therapy with cinacalcet or total or subtotal parathyroidectomy could be initiated as an alternative to switching lithium to a different mood stabilizer in patients who have maintained stability with long term lithium treatment.[49]

Other reported side effects

Cognitive impairment

Lithium has been shown to have a beneficial effects on improving cognition.[50] Cognitive impairment and mental slowness that are observed with lithium treatment seems to be related to the effects of mood instability rather than being a direct effects of lithium. It has been shown that bipolar illness predispose patients to cognitive dysfunction, which are exacerbated during acute episodes of the mania or depression. Some patients who are at risk of developing cognitive impairment may require maintenance on the lowest effective lithium concentration level.[51]

Serotonin syndrome

Serotonin syndrome, which is a potentially life-threatening condition could be precipitated by lithium. The signs and symptoms of serotonin syndrome may include autonomic instability manifested by tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia; and neuromuscular symptoms including tremor, rigidity, myoclonus, hyperreflexia, incoordination, seizures; and gastrointestinal symptoms of nausea, vomiting and diarrhea. It could also be manifested by mental status changes such as agitation, hallucinations, delirium, and coma. The risk of serotonin syndrome is increased with the concomitant use of other serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants (TCAs), fentanyl, tramadol, tryptophan, buspirone, St. John's Wort, and the mono amino oxidase inhibitors (MAOIs).[52] Monitoring patients for the emergence of serotonin syndrome, discontinuation of the precipitating agents, and prompt initiation of supportive symptomatic treatment are important prudent tenants of the clinical practice of lithium therapy. If concomitant use of lithium with other serotonergic drugs is clinically

warranted, patients should be educated and informed about the increased risk for serotonin syndrome and on developing strategies to monitor any emergence of its symptoms.

Encephalopathic syndrome

Encephalopathy is a rare drug interaction that have been reported to occur between lithium and certain antipsychotic medications such as haloperidol and risperidone. The encephalopathic syndrome is characterized by altered mental state with impairment of the cognition, attention, orientation, sleep–wake cycle and consciousness. It could be accompanied by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, and elevated serum liver enzymes. Although a causal relationship between the concomitant administration of lithium and antipsychotics has only been reported in case studies,[53] patients receiving such combined treatment should be monitored closely for early evidence of encephalopathy which would prompt treatment discontinuation and immediate emergency medical intervention.

Lithium intoxication

The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic range (0.8 to 1.2mEq/L). Some patients may exhibit toxic signs at serum concentrations that are considered within the therapeutic range. Lithium may take up to 24 hours to distribute into brain tissue, so occurrence of acute toxicity symptoms may be delayed. Neurological signs of lithium toxicity range from mild neurological adverse reactions such as fine tremor, lightheadedness, lack of coordination, and weakness; to moderate manifestations like giddiness, apathy, drowsiness, hyperreflexia, muscle twitching, ataxia, blurred vision, tinnitus, and slurred speech; and severe manifestations such as clonus, confusion, seizure, coma, and death. In rare cases, neurological sequelae may persist despite discontinuing lithium treatment and may be associated with cerebellar atrophy. Cardiac manifestations involve electrocardiographic changes, such as prolonged QT interval, ST and T-wave changes and myocarditis. Renal manifestations include urine concentrating defect, nephrogenic diabetes insipidus, and renal failure. Lithium intoxication may be caused by different factors including: intentional or accidental overdose; alterations in lithium excretion secondary to concomitant medication, a consequence of dehydration or infections, and fever.[54] Due to the potential severe complications of lithium toxicity, clinicians are behooved to exert focused care and vigilant monitoring of lithium level and the emergence of unanticipated adverse effects. Clinician should pay closer attention to older patients, who are more vulnerable to lithium intoxication

at far lower levels than younger patients. Additionally, lithium-treated patients should be regularly monitored for the risk factors of lithium toxicity which may include recent onset of concurrent febrile illness, concomitant administration of agents affecting lithium levels as summarized in table 1, and the presence of impaired renal functions. Lithium toxicity may occur in neonates who were exposed to lithium in late pregnancy. A floppy baby syndrome including neurological, cardiac, and hepatic abnormalities that are similar to those seen with lithium toxicity in adults have been observed. Symptoms include hypotonia, respiratory distress syndrome, cyanosis, lethargy, feeding difficulties, depressed neonatal reflexes, neonatal depression, apnea, and bradycardia. Monitoring neonates and providing medical supportive care is necessary until reversal of all toxic signs, which may take up to 14 days.

Lithium clinical indications

Collectively and worldwide, most clinical guidelines consider lithium as the most robust and first-line intervention for maintenance treatment of bipolar disorder. It is considered to be the most effective treatment for mania, with relatively modest support for the management of acute bipolar depression.[55] There is also a general consensus across various guidelines that lithium tangibly reduces the risk of suicide even if mood stabilization is not achieved and serum lithium levels are lower than the conventionally accepted therapeutic blood level ranges.[56] Although antidepressants are the first-line treatment option for patients with moderate to severe depression, many do not respond adequately to antidepressants and are described as having treatment-resistant depression (TRD).[57] Lithium is considered an effective augmenting agent for the management of TRD.[58,59] Lithium also possess neuroprotective effects and the ability to slow or even stop neuronal loss, which may also benefit patients with cognitive disorders.[60] Recent studies have also shown that lithium has the potential for the treatment of many other neurodegenerative disorders, including Alzheimer's,[61] Parkinson's[62] and Huntington's[63] disease, through its neurotrophic, neuroprotective, antioxidant and anti-inflammatory actions.

SUMMARY

The mechanism of action of lithium is complex. Along with its various formulations, judicial dosing and frequent monitoring are required. Its broad clinical utility are multi-faceted, encompassing mood stability, antidepressants augmentation in treatment resistant depression, suicide prevention, and neuroprotective properties. Its use in bipolar disorder is remarkably underutilized, particularly as it has the best evidence for the treatment of acute bipolar mania,

bipolar depression, and prevention of episodes of mood instability associated with bipolar disorder, qualifying it perhaps as the only currently available true mood stabilizer[64]. Clinicians caring for 21st century psychiatric patients with bipolar disorder are behooved to rekindle and harness their knowledge about this valuable therapeutic intervention. Abandoning lithium in today's clinical practice, would deprive myriad of patients from experiencing its benefits in minimizing their mental sufferings and disabilities.

Conflict of interest statement

The authors report no conflicts of interest. The materials described in this manuscript are those of the authors and do not reflect the views of the Department of Veterans Affairs or the VA Central California Health Care System or the Department of Psychiatry of UCSF -Fresno medical Education Program or Fresno County Department of Behavioral Health.

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