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Review Article

Bipolar Disorders and Lithium: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Indications of Lithium: Review of Articles

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Abstract

Lithium is a mood stabilizer which is approved for use in acute and maintenance mania. It is the first medications approved for the treatment of bipolar disorders. The drug has narrow therapeutic index 0.6-1.2meq/l.

The specific mechanism of action of lithium in stabilizing mood is unknown. Alters sodium transport across cell membranes in nerve and muscle cells, It alters metabolism of neurotransmitters including catecholamines and serotonin. May alter intracellular signaling through actions on second messenger systems. Specifically, inhibits inositol monophosphatase, possibly affecting neurotransmission *via* phosphatidyl inositol second messenger system. Also reduces protein kinase C activity, possibly affecting genomic expression associated with neurotransmission.

Common side effects include tremor, nausea, fatigue, increased thirst and slowed thinking. Important Serious side effects include hypothyroidism, weight gain and diabetes insipidus, and lithium toxicity. Blood level monitoring is recommended to decrease the risk of potential toxicity. There is an increased risk of fetal abnormalities if lithium is taken in pregnancy. Lithium concentrations are known to be increased with concurrent use of diuretics especially loop diuretics (such as furosemide) and thiazides and Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) such as ibuprofen, ACE inhibitors such as captopril, enalapril, and lisinopril. Its level decrease when used with drugs includes theophylline, caffeine, and acetazolamide. Concurrent use of lithium with antidepressants and antipsychotics may associate with serotonin syndrome and neuroleptic malignant syndrome respectively.

Keywords: Lithium; Pharmacokinetics; Pharmacodynamics; Side effects; Drug interactions

Introduction

Lithium, which is an effective mood stabilizer, is approved for the treatment of mania and the maintenance treatment of bipolar disorder. It is the "classic" mood stabilizer, the first to be approved by the US FDA, and still popular in treatment. The efficacy of lithium for treating mania was discovered in 1949, making it the first medication specifically developed to treat bipolar disorder [1,2]. Lithium remains a mainstay of treatment for bipolar disorder, especially for acute mania and maintenance treatment. In addition, lithium appears to reduce the risk of suicide in patients with bipolar disorder [3].

History and uses of lithium

Lithium is the third element of the periodic table and is a monovalent cation that shares certain properties with sodium, potassium, and calcium. Lithium is the only medication to reduce suicide rate [4-6]. It decreases rate of completed suicide in 15% of bipolar patients [3,7-10]. It is effective in long-term prophylaxis of both mania and depressive episodes in 70% of bipolar I patients. Factors predicting positive response to lithium include prior response or family member with good response, classic pure mania and mania is followed by depression. It is an effective mood stabilizer approved for the treatment of mania and the maintenance treatment of bipolar disorder. The main use of lithium is in the treatment of acute mania and prophylaxis of bipolar disorder relapses, however it also has indications in other psychiatric conditions such as treatment resistant depression, schizoaffective disorder and schizophrenia [1,2,6].

Lithium is simple inorganic ion. It occurs naturally in animal tissue but has no known physiological function. Lithium has very low therapeutic index. Sodium depletion and dehydration can decrease renal excretion of lithium thus leading to lithium toxicity [4-6]. Lithium not only treats acute episodes of mania and hypomania but was the first psychotropic agent shown to prevent recurrent episodes of illness. Lithium may also be effective in treating and preventing episodes of depression in patients with bipolar disorder. It is least effective for rapid cycling or mixed episodes. Furthermore, many patients are unable to tolerate it because of numerous side effects, including gastrointestinal symptoms such as dyspepsia, nausea, vomiting, and diarrhea, as well as weight gain, hair loss, acne, tremor, sedation, decreased cognition, and in co-ordination. There are also long-term adverse effects on the thyroid and kidney. Lithium has a narrow therapeutic window, requiring monitoring of plasma drug levels [7,11].

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It is FDA approved for effective antimanic, mood stabilization and bipolar depression treatments. If discontinued relapse near 100% in 2 years. Therapeutic level of lithium is 0.6-1.2meq/L, when exceed that 1.5, seriously toxicity begins to start. Maintenance drug level 0.4-8meq/l [1-4,6]. Lithium was used during the 19th century to treat gout. Lithium salts such as lithium carbonate (Li2CO3), lithium citrate, and lithium orotate are mood stabilizers. They are used in the treatment of bipolar disorder, since unlike most other mood altering drugs, they counteract both mania and depression. Lithium can also be used to augment other antidepressant drugs. It is also sometimes prescribed as a preventive treatment for migraine disease and cluster headaches. The active principle in these salts is the lithium ion Li+, which having a smaller diameter, can easily displace K+ and Na+ and even Ca+2, in spite of its greater charge, occupying their sites in several critical neuronal enzymes and neurotransmitter receptors [12-15].

Mechanism of action of lithium (pharmacodynamics)

The specific biochemical mechanism of lithium action in stabilizing mood is unknown. Alters sodium transport across cell membranes in nerve and muscle cells, It alters metabolism of neurotransmitters including catecholamines and serotonin. May alter intracellular signaling through actions on second messenger systems. Specifically, inhibits inositol monophosphatase, possibly affecting neurotransmission *via* phosphatidyl inositol second messenger system. Also reduces protein kinase C activity, possibly affecting genomic expression associated with neurotransmission. Increases cytoprotective proteins, activates signaling cascade utilized by endogenous growth factors, and increases gray matter content, possibly by activating neurogenesis and enhancing trophic actions that maintain synapses [16-24]. One mechanism is the drug modulates synaptic transmission mediated by monoamine neurotransmitters, accelerates presynaptic destruction of Catecholamine's, inhibits transmitter release at the synapses and decreases post synaptic receptor sensitivity (NE, DA, Serotonin) [24].

Serotonin neurotransmission: Lithium may also increase the release of serotonin by neurons in the brain. *In vitro* studies performed on serotonergic neurons from rat raphe nuclei have shown that when these neurons are treated with lithium, serotonin release is enhanced during a depolarization compared to no lithium treatment and the same depolarization. Lithium may increase the release of serotonin to the synapse, perhaps by inhibiting 5-HT1A and 5-HT1B auto receptors. According to different evidences this effect of lithium is responsible for antidepressant effects of lithium [18]. Inhibition of Phospho Adenine Phosphate (PAP) phosphatase: PAP phosphatase is an enzyme which metabolizes phosphate group from PAP. Lithium Inhibit of Phospho Adenine Phosphate (PAP) phosphatase. This hypothesis was supported by the low Ki of lithium for human PAP-phosphatase compatible within the range of therapeutic concentrations of lithium in the plasma of people (0.8–1 mM). Importantly, the Ki of human pAp-phosphatase is ten times lower than that of GSK3β (glycogen synthase kinase 3β). Inhibition of PAP-phosphatase by lithium leads to increased levels of pAp (3′-5′ phosphoadenosine phosphate), which was shown to inhibit PARP-1[24-26]. Glutamate neurotransmission: Another mechanism proposed in 2007 is that lithium may interact with Nitric Oxide (NO) signaling pathway in the central nervous system, which plays a crucial role in the neural plasticity. The NO system could be involved in the antidepressant effect of lithium in the forced swimming test in mice. It was also reported that NMDA receptor blockage augments antidepressant-like effects of lithium in the mouse forced swimming test, indicating the possible involvement of NMDA receptor/NO signaling in the action of lithium in this animal model of learned helplessness. Glutamate levels are observed to be elevated during mania. Lithium is thought to provide long-term mood stabilization and have anti-manic properties by modulating glutamate levels. It is proposed that lithium competes with magnesium for binding to NMDA glutamate receptor, increasing the availability of glutamate in postsynaptic neurons. The NMDA receptor is also affected by other neurotransmitters such as serotonin and dopamine. Effects observed appear exclusive to lithium and have not been observed by other monovalent ions such as rubidium and caesium [24].

Dopamine neurotransmission: During mania, there is an increase in neurotransmission of dopamine that causes a secondary homeostatic down-regulation, resulting in decreased neurotransmission of dopamine, which can cause depression. Additionally, the post-synaptic actions of dopamine are mediated through G-protein coupled receptors. Once dopamine is coupled to the G-protein receptors, it stimulates other secondary messenger systems that modulate neurotransmission. Studies found that in autopsies (which do not necessarily reflect living people), people with bipolar disorder had increased G-protein coupling compared to people without bipolar disorder [24]. Lithium treatment alters the function of certain subunits of the dopamine associated G-protein, which may be part of its mechanism of action [24].

GABA neurotransmission: GABA is an inhibitory neurotransmitter that plays an important role in regulating dopamine and glutamate neurotransmission. It was found that patients with bipolar disorder had lower GABA levels, which results in excitotoxicity and can cause apoptosis (cell loss). Lithium counteracts these degrading processes by decreasing pro-apoptotic proteins and stimulating release of neuroprotective proteins [24].

Cyclic AMP secondary Messengers: The Cyclic AMP secondary messenger system is shown to be modulated by lithium. Lithium was found to increase the basal levels of cyclic AMP but impair receptor coupled stimulation of cyclic AMP production [24]. It is hypothesized that the dual effects of lithium are due the inhibition of G-proteins that then mediate cyclic AMP production. Over a long period of lithium treatment, Cyclic AMP and adenylate cyclase levels are further changed by gene transcription factors [24].

Ion transport theories: make use of lithium's similarities to both monovalent (sodium, potassium) and divalent (calcium, magnesium) cations to focus on ion pumps and channels in cell membranes. For example, some investigators have found altered levels of sodium, potassium-adenosine triphosphatase (Na, K-ATPase) activity in patients with bipolar disorder. Since neuronal transmembrane potential differences are maintained by the Na, K-ATPase pump (also known as the sodium pump), perturbations of this system are felt to cause neurotransmitter aberrations that translate into mania and depression. Because lithium crosses cell membranes by four independent mechanisms (sodium pump, sodium leak channel, sodium- lithium counter transport, and lithium –bicarbonate exchange), it is possible that it could stabilize membrane function

Table 1: Summary of pre lithium work up and monitoring.

Thyroid Function tests:	TSH and T4 at baseline and yearly because it can cause hypothyroidism
Complete blood count:	Baseline and if symptoms arise lithium can cause leucocytosis
Electrolytes:	Baseline, yearly, and if symptoms arise and avoid prescribing lithium in
Hydrations	Dehydrated or sodium-depleted patients due to it increases risk of lithium toxicity
Serum lithium level:	Twice per week until serum concentrations and clinical condition have stabilized, then at least every three months and if symptomatic. Check more frequently if used with nsaids fluoxetine check when patients initiate or discontinue acei/arb or diuretic (avoid concomitant use if possible. Monitor closely if used with metronidazole of
Pregnancy test:	In women of childbearing potential, at baseline and if suspected due to it may be teratogenic during first trimester(the first trimester is associated with Ebstein's anomaly population)1/1000 (20X greater risk than the general
Renal function:	Serum creatinine, BUN, urinalysis, and urine specific gravity or osmolality at baseline, yearly, and if symptoms arise due to renal function can affect lithium levels; lithium can affect renal function
Monitoring	Steady state achieved after 5 days- check 12 hours after last dose.
	Once stable check lithium level every 3 months and TSH and creatinine every 6 months.
Goal:	Blood level between 0.6-1.2

through such an interaction. Synapse-specific accumulation of lithium has been demonstrated in intracellular micro domains. In addition in 2014, it was proposed that lithium treatment works by affecting calcium signaling by blocking excitotoxic processes such as antagonizing N-methyl-d-aspartate (NMDA) receptors and inhibiting Inositol Monophosphatase (IMPase) [24,27].

Inositol depletion hypothesis: Lithium treatment has been found to inhibit the enzyme inositol monophosphatase, involved in degrading inositol monophosphate to inositol required in PIP2 synthesis. This leads to lower levels of inositol triphosphate, created by decomposition of PIP2. This effect has been suggested to be further enhanced with an inositol triphosphate reuptake inhibitor. Inositol disruptions have been linked to memory impairment and depression. It is known with good certainty that signals from the receptors coupled to the phosphoinositide signal transduction is effected by lithium. Myo-inositol is also regulated by the high affinity Sodium Mi Transport System (SMIT). Lithium is hypothesized to inhibit mI entering the cells and mitigating the function of SMIT. Reductions of cellular levels of myo-inositol results in the inhibition of the phosphoinositide cycle [24-26].

Pharmacokinetics of lithium: Lithium is rapidly and completely absorbed, with serum concentrations peaking in 1 to 1.5 hours with standard preparations and in 4 to 4.5 hours with the slow and controlled release forms. Unlike most psychiatric drugs, lithium has no clinically important protein binding properties and no metabolites. It is excreted almost entirely by the kidneys, although small amounts are also lost in sweat and feces. A substantial amount of filtered lithium is reabsorbed (primarily in the proximal tubules), so that renal lithium clearance is about one fifth of creatinine clearance. The elimination half-life of lithium is about 18 to 24 hours, although it is considerably longer in the elderly because of the age-related decrease in Glomerular Filtration Rate (GFR) (and correspondingly shorter in youth for the opposite reason. Lithium is not liver metabolized. It is excreted through kidney. The drug is not protein bound and 70-80% reabsorbs proximal tubule of the kidney. Its level increase with decrease in serum level of sodium ion especially during dehydration, administration with thiazide diuretics. It has half-life of 24 hrs with steady state of 5 days. Plasma peak Levels concentration of lithium reaches in 2 hrs [2,24].

Pre lithium work up and monitoring: Before starting lithium treatment we need to get baseline creatinine, TSH, CBC and ECG for age greater than 40 years. In women check a pregnancy test due to lithium use during the first trimester is associated with Ebstein's anomaly 1/1000 (20X greater risk than the general population). Those who use lithium should receive regular serum level tests and should monitor thyroid and kidney function for abnormalities, as it interferes with the regulation of sodium and water levels in the body, and can cause dehydration. Dehydration, which is compounded by heat, can result in increasing lithium levels. The dehydration is due to lithium inhibition of the action of antidiuretic hormone, which normally enables the kidney to reabsorb water from urine. This causes an inability to concentrate urine, leading to consequent loss of body water and thirst [28-31]. Lithium concentrations in whole blood, plasma, serum or urine may be measured using instrumental techniques as a guide to therapy, to confirm the diagnosis in potential poisoning victims or to assist in the forensic investigation in a case of fatal over dosage. Serum lithium concentrations are usually in the 0.5–1.3 mmol/l range in well-controlled people, but may increase to 1.8–2.5 mmol/l in those who accumulate the drug over time and to 3–10 mmol/l in acute overdose [28-42]. Lithium salts have a narrow therapeutic/toxic ratio, so should not be prescribed unless facilities for monitoring plasma concentrations are available. Doses are adjusted to achieve plasma concentrations of 0.4 to 1.2 mmol Li+/l (lower end of the range for maintenance therapy and the elderly, higher end for children) on samples taken 12 hours after the preceding dose [36-42] (Table 1).

Predictors of good lithium response: Factors predicting positive response to lithium includes prior response or family member with good response, classic pure mania and mania is followed by depression [36-42].

Summary of predictors for good lithium response

1. Past Lithium response (personal or family)
2. Euphoric, pure (classic) mania
3. Sequence Mania-Depression -Euthymia
4. No psychosis
5. No Rapid Cycling

Table 2: Adverse effects of lithium [36-40].

Very Common adverse effects of lithium include (>10% incidence)	Headache
	Hyperreflexia — over responsive reflexes.
	Leukocytosis — elevated white blood cell count
	Muscle weakness (usually transient, but can persist in some)
	Myoclonus — muscle twitching.
	Nausea (usually transient, but can persist in some)
	Polydypsia — increased thirst.
	Polyuria — increased urination.
	Vomiting (usually transient, but can persist in some)
	Vertigo
	Weight gain
	Confusion
	Constipation (usually transient, but can persist in some)
	Decreased memory
	Diarrhea (usually transient, but can persist in some)
	Dry mouth
	EKG changes — usually benign changes in T waves.
	Hand tremor (usually transient, but can persist in some)
Common (1-10%) adverse effects	Hypothyroidism — a deficiency of thyroid hormone.
	Hair loss/hair thinning
	Acne
	Extrapyramidal side effects — movement-related problems such as muscle rigidity, parkinsonism, dystonia, etc.
	Euthyroid goitre — i.e. the formation of a goitre despite normal thyroid functioning.
Rare/Uncommon (<1%) adverse effects include	Myasthenia gravis — an autoimmune condition where the body's own defences attack the neuromuscular junction — the gap across which the nerves communicate with the muscles — leading to muscle weakness.
	Oedema
	Pseudotumor cerebri
	Renal (kidney) toxicity which may lead to chronic kidney failure
	Renal interstitial fibrosis
	Seizure
	Sinus node dysfunction
	Transient reduction in peripheral circulation as a whole
	Brugada syndrome — a potentially fatal abnormality in the electrical activity of the heart.
	Coma
	Erythema multiforme — a potentially fatal skin reaction
	Hallucinations
	Hypercalcaemia — elevated blood levels of calcium.
	Hypermagnesaemia — elevated blood levels of magnesium.
	Hyperparathyroidism — elevated blood levels of parathyroid hormone.
	Hyperthyroidism — elevated blood concentrations of thyroid hormones.
	Increased intracranial pressure and papilledema
Unknown frequency adverse effects include	Nystagmus — involuntary eye movements that can interfere with vision.
	Oliguria — low urine output, although excess urine output is more likely.
	Sexual dysfunction including impotence, decreased libido, vaginal dryness, erectile dysfunction, etc.
	Slurred speech
	Somnolence

	Weight loss (gain is more common with prolonged treatment) Abdominal pain
	Albuminuria — protein in the urine, a sign of impaired kidney function.
	Bradycardia — low heart rate.
	Changes in taste
	Decreased creatinine clearance — another sign of impaired kidney function.
	Flatulence
	Gastritis
	Glycosuria — glucose (blood sugar) in the urine.
	Hyperthermia
	Hypotension — low blood pressure.
	Indigestion

Predictors of poor Li response [Good response to anticonvulsants]

1. Mixed mania (adolescents)
2. Irritable mania
3. Secondary mania (geriatric)
4. Psychotic Symptoms
5. Rapid Cycling
6. Depression-Mania-Euthymia
7. Comorbid substance abuse

Side effects of lithium

Thyroid a abnormalities (Hypothyroidism): Transient mild abnormalities in thyroid function testing are common early in the course of lithium treatment but are usually of little or no clinical consequence. Some patients, however, develop goiter or clinical hypothyroidism sometime during the course of treatment. Women, those with preexisting thyroid dysfunction and those from iodine deficient areas, are more than usually susceptible. Among lithium's many effects on thyroid function, most importantly it impedes the release of hormone from the gland. The goiter that has been described in about 5 percent of patients taking lithium prevalence figures vary widely) is rarely of cosmetic or obstructive importance; however, an ultrasound study found thyroid gland enlargement in 44 percent of patients on lithium for 1 to 5 years in contrast to 16 percent of a control group [42-47].

Clinical hypothyroidism occurs in at least 4 percent of patients taking lithium (there is considerable variation in prevalence ranging 4 to 39.6 percent). Once diagnosed, it can be treated with supplemental levothyroxine at a dosage that returns the TSH concentration to normal. Subclinical hypothyroidism (elevated TSH, normal free thyroxine) is considerably more common than clinical hypothyroidism. Substantial elevations of TSH are likely to progress to clinical hypothyroidism and thus should be treated with exogenous thyroid hormone. Minor elevations, on the other hand, especially early in the course of lithium. Therapy are likely to normalize without treatment. Nonetheless, subclinical hypothyroidism may not be asymptomatic, and it may be associated with a slower response of bipolar depression to conventional treatment; consequently it may require treatment with supplemental thyroxine [42-47].

Lithium induced weight gain: Weight gain is a common adverse effect of lithium and may be due to the drugs complex effects on carbohydrate metabolism. Lithium is known to be responsible for 1–2 kg of weight gain. Weight gain may be a source of low self-esteem for the clinically depressed. Most side effects of lithium are dose-dependent. The lowest effective dose is used to limit the risk of side effects. weight gain is more common with prolonged treatment [42,43].

Pregnancy and breast feeding: Lithium is the mood stabilizer with the least reported increase in birth defects for women requiring a mood stabilizer during pregnancy [51]. Use of lithium in first trimester pregnancy associated with an increase in cardiac defects, particularly Epstein's anomaly which is increased from 1: 10-20,000 to 1: 1000. Lithium is transmitted in highly variable concentrations in the breast milk (30%-80% or more) It may cause lethargy, drowsiness, cardiac, thyroid and other side effects on child [51,52]. Lithium is a teratogen, causing birth defects in a small number of newborn babies. Several retrospective studies have demonstrated possible increases in the rate of a congenital heart defect known as Epstein's anomaly [52], if taken during a woman's pregnancy. As a consequence, fetal echocardiography is routinely performed in pregnant women taking lithium to exclude the possibility of cardiac anomalies. Lamotrigine seems to be a possible alternative to lithium in pregnant women. Gabapentin and clonazepam [53] are also indicated medications during the child bearing years and during pregnancy [54]. Valproic acid and carbamazepine also tend to be associated with teratogenicity [55].

Lithium and dehydration: Dehydration in people taking lithium salts can be very hazardous, especially when combined with lithium-induced nephrogenic diabetes insipidus with polyuria. Such situations

Table 3: Summary of levels of lithium Intoxication.

Severity	Range (serum lithium level)	Symptoms
Mild	1.5-2.0	vomiting, diarrhea, ataxia, dizziness, slurred speech, nystagmus.
Moderate-	2.0-2.5	nausea, vomiting, anorexia, blurred vision, clonic limb movements, convulsions, delirium, syncope
Severe	>2.5	generalized convulsions, oliguria and renal failure

include preoperative fluid restrictions, warm weather conditions, sporting events, hiking, or other periods of fluid inaccessibility. Dehydration can result in increased plasma lithium levels due to decreased glomerular filtration rate, which causes lithium retention. Further, in the case of diabetes insipidus, free water is lost in greater proportion to sodium and other electrolytes, artificially raising lithium's concentration in the blood. Another danger is that if the period of dehydration and diuresis has been prolonged, total body stores of sodium may actually be depleted, despite elevated plasma levels. Thus, rapid hydration with a large volume of plain water may very quickly produce hyponatremia, as total stores of sodium may be insufficient to support normal concentrations at a normal blood volume. Rapid overcorrection of hypernatremia also increases the risk of developing cerebral edema. Hyponatremia can also promote lithium retention by increasing reabsorption in the distal nephron, thus increasing lithium levels [56] (Table 2).

Lithium Intoxication: Lithium intoxication is primarily a neurotoxicity that can lead to death or permanent neurological damage (often cerebellar as characterized by dysarthric speech, tremor, and wide-based gait). Cardiovascular, gastrointestinal, and renal manifestations may also be present. Factors associated with toxicity include excessive intake (accidental or deliberate), reduced excretion, kidney disease, low-sodium diet, drug interaction, reduced volume of distribution (dehydration), and individual sensitivity (the elderly and the organically impaired). Lithium toxicity may occur on an acute basis, in persons taking excessive amounts either accidentally or intentionally, or on a chronic basis, in people who accumulate high levels during ongoing therapy. The manifestations include nausea, emesis, diarrhea, asthenia, ataxia, confusion, lethargy, polyuria, seizures and coma. Other toxic effects of lithium include coarse tremor, muscle twitching, convulsions and renal failure. People who survive a poisoning episode may develop persistent neurotoxicity. Several authors have described a "Syndrome of Irreversible Lithium-Effected Neurotoxicity" (SILENT), associated with episodes of acute lithium toxicity or long-term treatment within the appropriate dosage range. Symptoms are said to include cerebellar dysfunction. Overdosage, usually with plasma concentrations over 1.5 mmol Li+/l, may be fatal, and toxic effects include tremor, ataxia, dysarthria, nystagmus, renal impairment, confusion and convulsions. If these potentially hazardous signs occur, treatment should be stopped, plasma lithium concentrations redetermined, and steps taken to reverse lithium toxicity [57]. Lithium toxicity is compounded by sodium depletion. Concurrent use of diuretics that inhibit the uptake of sodium by the distal tubule (e.g. thiazides) is hazardous and should be avoided because this can cause increased resorption of lithium in the proximal convoluted tubule, leading to elevated, potentially toxic levels. In mild cases, withdrawal of lithium and administration of generous amounts of sodium and fluid will reverse the toxicity. Plasma concentrations in excess of 2.5 mmol Li+/l are usually associated with serious toxicity requiring emergency treatment. When toxic concentrations are reached, there may be a delay of one or two days before maximum toxicity occurs [57].

In long-term use, therapeutic concentrations of lithium have been thought to cause histological and functional changes in the kidney. The significance of such changes is not clear, but is of sufficient concern to discourage long-term use of lithium unless it is definitely indicated. Doctors may change a bipolar patient's medication from lithium to another mood-stabilizing drug, such as valproate, if problems with the kidneys arise. An important potential consequence of long-term lithium use is the development of renal diabetes insipidus (inability to concentrate urine). Patients should therefore be maintained on lithium treatment after three to five years only if, on assessment, benefit persists. Conventional and sustained-release tablets are available. Preparations vary widely in bioavailability, and a change in the formulation used requires the same precautions as initiation of treatment. There are few reasons to prefer any one simple salt of lithium; the carbonate has been the more widely used, but the citrate is also available [57] (Table 3).

Lithium induced hypercalcemia and hyperparathyroidism: Several possible mechanisms (antagonism of the calcium sensing receptor, direct stimulation of parathyroid hormone production, and decreased renal calcium excretion), lithium can cause hypercalcemia and hyperparathyroidism. Hypercalcemia associated with Lithium-Induced Hyperparathyroidism (LIH) is a common, but easily overlooked, complication of lithium treatment. Approximately 15% to 60% of patients receiving long term lithium treatment show elevated calcium levels (hypercalcemia), although only a few of these patients also have significant elevations of PTH levels and clinical symptoms of hyperparathyroidism. Interestingly, lithium-associated clinical hyperparathyroidism is almost always caused by a single parathyroid adenoma rather than 4-gland hyperplasia. Hypercalcemia is usually mild, but there have been reports of surgery being required to treat parathyroid hyperplasia or adenoma. Evidences indicated that longer duration of treatment is associated with an increased incidence of Lithium-Induced Hyperparathyroidism (LIH) [58-62].

Drug interactions

Diuretics: Thiazide diuretics decrease renal lithium clearance and increase the serum lithium concentration and lithium toxicity has been known to occur. If a thiazide is prescribed, lithium dosage reduction is often necessary. If a thiazide is discontinued, lithium dosage may need to be increased to avoid sub therapeutic levels. Although less well established, potassium-sparing diuretics may also cause lithium retention. On the other hand, loop diuretics such as furosemide (Lasix) do not reduce and may actually increase renal lithium clearance. Osmotic and xanthine diuretics (caffeine, theophylline and aminophylline) also increase lithium clearance. Because diuretics are often given to patients who are medically ill with unstable fluid-electrolyte status, interactions with lithium may not be predictable, and close monitoring is advised [36].

Anti-Inflammatory Drugs and ACE inhibitors: Most nonsteroidal anti-inflammatory drugs reduce renal lithium clearance and increase the serum lithium concentration in a way that is clinically important and potentially dangerous. Among the drugs that cause this interaction are indomethacin, phenylbutazone, diclofenac, ketoprofen, meloxicam, oxyphenbutazone, ibuprofen, piroxicam, and naproxen. Aspirin and possibly sulindac appear to be exceptions. Lithium concentrations can also be increased with concurrent use of ACE inhibitors such as captopril, Enalapril and lisinopril [36,63].

Other drug interactions: There are also drugs that can increase the clearance of lithium from the body, which can result in decreased lithium levels in the blood. These drugs include theophylline,

caffeine, and acetazolamide. Additionally, increasing dietary sodium intake may also reduce lithium levels by prompting the kidneys to excrete more lithium [64,65]. Lithium is also known to be a potential precipitant of serotonin syndrome in people concurrently on serotonergic medications such as antidepressants, buspirone and certain opioids such as pethidine, tramadol, oxycodone, fentanyl and others. Lithium co-treatment is also a risk factor for neuroleptic malignant syndrome in people on antipsychotics and other antidopaminergic medications [36,66,67]. High doses of haloperidol, fluphenazine, or flupenthixol may be hazardous when used with lithium; irreversible toxic encephalopathy has been reported [68].

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