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Review Article

ADVERSE DRUG REACTION OF LITHIUM CARBONATE-A REVIEW

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ABSTRACT

This study aims to review Lithium-associated ADRs during the treatment and its management. Databases of "Medline", "Google Scholar" and "PubMed" were searched with keywords for studies on ADRs of Lithium. All studies involving safety, monitoring and management of adverse drug reactions of Lithium were included. Most of the studies have reported that up to 50 to 80% of patients develop ADRs on Lithium. Common initial ADRs that develops within 1 w to 6 w are polydipsia and polyuria taken together (50 to 70%) followed by tremors (30 to 60%). GI symptoms (upset, abdominal pain and diarrhoea) up to 30% are other commoner ADRs of Lithium therapy and they mostly disappear later. Weight gain (20 to 50%), Hypothyroidism (14-34%) and Nephrotic diabetes insipidus develop during the long term Lithium therapy. Most of the ADRs are produced even at therapeutic range (0.6–1.2 mEq/l). As serum level increase, i.e. above 1.5 mEq/l, other serious ADRs like muscle fasciculation's, worsening of tremor, dysarthria, ataxia, EPS, hallucination, and visual disturbances, seizures, coma, and death may be expected. Management of ADRs includes TDM, Dose reduction of Lithium, drugs like diuretics, beta blockers, SR preparations and sometimes withdrawal of the drug. We are concluded that Lithium can cause many ADRs depending upon dose and duration of therapy, hence, the Therapeutic Drug Monitoring of Lithium is necessary.

Keywords: Lithium, ADR, Bipolar disorder, TDM

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INTRODUCTION

Adverse Drug Reaction (ADR) is defined as "Any noxious change, which is suspected to be due to the drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug" [1]. In general, adverse drug reactions of drugs are considered among the leading causes of morbidity and mortality all over the world. Adverse drug reaction associated with medication may vary for each individual depending on the illness state, age, weight, sex, ethnicity, general health, comorbid conditions, and use of other medications. In general, medication-induced adverse drug reaction more experience in the older patient because of the age-related change in pharmacodynamics, pharmacokinetics, metabolism, and excretion. In this review, we focus on Lithium, as the most prescribed mood-stabilizing drug in the treatment of bipolar disorder. Lithium is a small monovalent cation, which is one of the Mood stabilising drug widely used for acute treatment and maintenance of mania and depression, over 50 y. In 1970, it has been approved by FDA for the treatment of manic-depressive illness. Since it has still mainstay treatment option for the treatment of bipolar disorder for protecting against both mania and depression and reducing the risk of suicide [2]. However, it has narrow therapeutic index may cause increased risk of intoxication and produced various adverse drug reaction during the treatment, hence frequently monitoring serum Lithium level is required. More common adverse drug reaction associated with Lithium therapy in the bipolar disorder include polydipsia, polyuria, tremor, gastrointestinal upset, weight gain, hypothyroidism and nephrotic diabetics insipidus etc. In this review, we are discussing various adverse drug reactions according to the system involved i.e. gastrointestinal, neurological, nephrogenic, endocrinal, cognitive, sexual, hematological, hepatogenic and teratogenic ADRs associated with Lithium therapy.

There are many research articles published on the adverse drug reactions on this drug. In this article, we discuss various ADRs of Lithium during the course of treatment and provide the recommendation for managing ADRs in clinical practice. The scope of this review might be helpful for psychiatrist and students while treating patients with bipolar disorder.

Studies were selected for inclusion in this review based on a comprehensive literature search initially using database "MEDLINE", "PubMed" and "Google Scholar". The search terms included "Lithium", "ADR", "Bipolar disorder", "TDM", "adverse drug effect", "pharmacovigilance", "side effects", "mania", "mood stabiliser". In addition, we included studies found by cross-referencing and searching reference lists in textbooks on bipolar disorder and using the 'related articles' function of Pubmed. We included all studies that reported data on ADRs in patients with Lithium in bipolar disorder until June 2016, with no specific start date specified. All international or national studies, literature review, case series, abstract, case reports were involving safety, monitoring, prevalence and clinical management of adverse drug reactions of Lithium were included; high-quality, recent reviews of major topics were included to supplement the primary studies.

Lithium can produce more common ADRs such as tremor, polyuria, polydipsia, weight gain, gastric upset include nausea, vomiting, loose stools, and cognitive impairment, cardiac or dermatological problems, neurological like drowsiness, dizziness, lethargy, and headache. Here, we discuss various ADRs associated with Lithium therapy. Research on adverse drug reaction of Lithium has been focused on various organ systems, including gastrointestinal, neurological, renal, endocrine, dermatological, cardiac, hematological and teratogenic. The prevalence of ADRs has been up to 81% associated with Lithium therapy [3]. Comparative studies revealed no significant difference in terms of adverse drug reaction between multiple and single dosing in patients with Lithium [4]. Most of the ADRs are dose dependent and transient in nature [5]. Data on the exact prevalence of each side effect are not available.

Polyuria

Polyuria is common adverse drug reaction of Lithium treatment in patients with bipolar disorder. Polyuria has been predicted to occur in 15-40% of all patients treated with Lithium [6]. Polyuria, defined as quantitively urine output greater than 3 litres daily (24-h). Early study found that 24-h urine volumes were increased and urinary osmolality was decreased in patients using Lithium concurrently with psychotropic medication [7]. More recently, it has been found that patients treated with both Lithium and unspecified psychotropic drugs had a lower urinary concentrating capacity and glomerular filtration rate than patients taking Lithium alone [8]. Most of the study has found that polyuria may occur within first to the second week of

initiation of Lithium therapy, but some study showed that polyuria may occur after one month of Lithium therapy. The mechanism of polyuria during Lithium therapy remains unclear. Recently, an animal study has shown that an effect of Lithium in the collecting duct of the rat to decrease the density of apical water channels (aquaporin-2), possibly explaining at least some of the Lithium-induced NDI [9]. Nocturia can be a useful marker of polyuria. Up to 68% of patients report at least 1 urination episode per night. Some animal studies have determined an effect of Lithium to stimulate thirst very early in the course of Lithium administration [10]. Long-term Lithium treatment was also associated with a higher risk of polyuria, but this was not statistically significant [7]. In some reported patients polyuria was also in part attributable to Lithium-induced polydipsia [11]. Polyuria may be persistent or disappear after few months of Lithium therapy. Reducing the Li+level may mitigate NDI; or a thiazide diuretic, which can paradoxically reverse polyuria by an incompletely understood mechanism. Polyuria can be treated with other medications, such as NSAID. Both thiazides and potassium-sparing diuretics have been shown to relieve Lithium-induced polyuria [12]. Reports suggest that the drug amiloride may be particularly beneficial for the treatment of Lithium-associated polyuria [13].

Polydipsia

Polydipsia is common adverse effect also associated with Lithium therapy. Primary polydipsia, also known as psychogenic polydipsia or compulsive water drinking, is an important clinical entity, affecting patients with severe psychiatric illness [2]. In one case report of persistent Lithium-induced NDI, the patient drank 20-40 glasses of water per day. The effect of chronic primary polydipsia to impair urinary concentrating ability in response to dehydration or vasopressin administration was documented several decades ago [14]. However, the molecular mechanisms responsible for this finding had not been elucidated. Polydipsia is treated as similar to polyuria.

Weight gain

Weight gain is more common ADR of long-term Lithium therapy [15–17]. In some studies, long-term Lithium therapy has been associated with modest but significant weight gain, appeared in between 3 mo to 1 y of initiation of Lithium therapy [15, 18]. A mean weight gain of more than 10 kg in 20% of patients on long-term therapy. Those who were obese at the start of the Lithium therapy were more prone to increases weight gain. In another some study investigated, mean weight gain of 3-7 kg in 50% of patients, who were on Lithium therapy, increase gradually over a period of 2-3 mo [17, 18]. In some study has reported, the weight of patients who were taking Lithium over a ten-year period, 11 to 65 % gained an average of 10 kg; weight gains of up to 27 kg have been reported with protracted exposure in a dose-dependent pattern [16]. The increase in body weight was statistically significant in both sexes male and female with a mean weight gain in women of 4.0 kg and 3.8 kg in men. When expressed as percentage body weight gain, there was a significant sex difference with higher percentage body weight gain in women [19]. Other Similar studies also found has more weight gain in women than in men under Lithium therapy [20, 21], while some other published studies report no sex difference in weight gain [15, 22]. It is not clear till if female sex alone is a vulnerability factor, or if gender-specific differences in lifestyle, food intake or eating behaviour might contribute to these findings. Nevertheless, body weight gain during Lithium therapy is might be of greater concern to female patients compared with men.

The mechanism for Lithium-induced weight gain without hypothyroidism is not known. Several explanations have been proposed. Lithium often increases thirst and may foster consumption of high-calorie liquids [15]. Lithium-induced edema may also be a contributor [23]. Controversial data suggest that Lithium increases storage of carbohydrates and lipids. Lithium has been reported to have insulin-like effects on carbohydrate metabolism. Changes in lipid metabolism, an increase in serum magnesium and calcium and changes in carbohydrate metabolism with increased glucose tolerance [24, 25]. Lithium-induced hypothyroidism could also explain weight accumulations [26]. Weight gain can be a problem with Lithium treatment, but it is less pronounced than with the most frequently prescribed 'atypical' neuroleptics [27].

Tremor

A drug-induced tremor is involuntary shaking due to the use of medication. Tremor is more common ADR of Lithium treatment in bipolar disorders [28]. It is important that tremor is one of the commoner reasons given by patients for discontinuing Lithium therapy. Tremor has been reported in up to 65% of patients using Lithium [29, 30]. Tremors occur in the first week during Lithium treatment, however, it subsided within the next week [31, 32]. Recently it has been found that tremor in patients on long-term treatment of Lithium therapy has a lower frequency than that of normal physiological tremor and is likely to have an extrapyramidal component [33]. Whenever tremor is extremely troublesome, reducing the Li+level may provide relief. Alternatively, beta blocker like propranolol in divided doses of 20 to160 mg daily may reduce the tremor. In rare cases, cessation of Li+therapy is required [34]. Extended-release preparations can reduce tremor. Reducing the use of caffeine and nicotine can have a positive effect. primidone and vitamin B6 may be added to help control the tremor [35]. As another psychotropic, in particular, selective serotonin reuptake inhibitors, may worsen postural tremor, their necessity must be re-evaluated.

Systemic ADRs

Gastrointestinal ADRs

Gastrointestinal ADRs included Nausea, diarrhoea, vomiting, abdominal discomfort, loose bowels, excess salivation and dyspepsia are more common during Lithium therapy in bipolar disorders [36]. These ADRs occurring in 20 to 50% of patients. Generally, those ADRs may also appear during the first week of Lithium therapy in bipolar disorders [18, 32]. Initial ADRs are often dose related and are worse at peak concentrations. These ADRs usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, cessation of Lithium therapy may be required. Standard treatments reduce the dose, taking the smaller dose with the meal, drugs can be taking at bedtime may helpful for reducing gastrointestinal ADRs. Using extended release preparation can reduce GIT adverse effect. A temporary reduction is the best management option if nausea occurs, followed by a more gradual increase dose. Persistent nausea can be treated with the histamine-2 antagonists, famotidine or cimetidine [37]. Diarrhoea, vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of Lithium intoxication and can occur at Lithium levels below 2.0 mEq/l.

Dermatological ADRs

Some common dermatological side effects are developed during Lithium therapy in bipolar patients. Acneform eruption, psoriasis, folliculitis, hair loss and maculopapular eruption, have been described as adverse reactions to Lithium therapy. Most patients observable dermatological ADRs as distressing, and without proper attention and treatment, there is an increased risk for poor compliance. Although a meta-analysis study showed no significant difference in the prevalence of skin disorders between patients administered Lithium and those given placebo [38]. In controlled trials study, 3.4–45% of patients treated with Lithium developed dermatological side effects, mainly acne and psoriasis [39]. Acne is one of the most common side effects; it can develop within weeks after initiation of Lithium treatment. The treatment for acne includes topical salicylic acid or tretinoin preparations [40]. Psoriasis may develop after a refractory period of a few weeks to several months. The incidence has been reported to be 1.8–6%. Pre-existing psoriasis should not be regarded as a contraindication to Lithium prescription, but patients with a positive family history of psoriasis should be monitored carefully [41]. Psoriasis in a patient using Lithium can be managed with topical steroids, vit-D analogs, keratolytic, or omega-3 fatty acids [42]. A serious rash as a symptom of Stevens–Johnson syndrome or toxic necrolysis was reported in 0.0 and 0.1% of patients, respectively. Hair loss (alopecia and telogen effluvium) and a change in the color and structure of the hair are rather common and distressing side effects of mood-stabilizing drugs. In a meta-analysis on Lithium toxicity, there was no significant increased risk of alopecia [38]. On long term use, Lithium

causes hair loss in at least 10% of patients [43]. If hair loss emerges, some authors recommend management without drug discontinuation: hair care techniques, trace mineral supplementation, treatment with minoxidil, and hair replacement pieces [44]. The therapeutic value of these measures remains unclear. Dose reduction or drug discontinuation almost always leads to complete hair regrowth [45].

Endocrine ADRs

Endocrine ADRs such as hypothyroidism and hyperparathyroidism are common during long-term Lithium treatment in bipolar patients [38,46]. The most sensitive indicator of hypothyroidism is a persistent and significant rise in serum thyrotrophin (TSH). Lithium inhibits thyroid hormone secretion by several different mechanisms. In the majority of patients, compensatory mechanisms operate and prevent the development of hypothyroidism. Some studies suggested that the risk of developing Lithium-induced hypothyroidism increases with the duration of treatment. The mean duration of Lithium treatment was relatively long, at 6.9 y. However, another study suggested, that the duration of treatment was not associated with an increase in the risk of developing hypothyroidism. Risk factors for the development of hypothyroidism include elevated thyroid autoantibody or TSH at baseline, family history, middle age, high Lithium concentration, an iodine deficiency and cigarette smoking [5]. The prevalence of thyroid autoantibodies among Lithium-treated patients varies across studies and may be more associated with the affective disorder than with Lithium [47]. Hypothyroidism is more common and is seen in more frequently in women than in man [48]. Women, especially those beyond the age of 40, more often present with thyroid autoimmunity [49], which renders them especially at risk for Lithium-induced hypothyroidism [50, 51]. Most patients are diagnosed with hypothyroidism in the first years of Lithium treatment [3, 52]. Many studies have been reported, That the wide range of prevalence rate of hypothyroidism of 0–34% in Lithium-treated patients [51, 53–56]. Up to 2% of Lithium-treated patients require treatment with levothyroxine [50,51]. Monitoring of the clinical symptoms provides useful guidance for the treatment, in addition to values of thyroid stimulating hormone or free T4, as management of even subclinical hypothyroidism may improve the outcomes among bipolar patients [57].

Renal ADRs

Lithium-induced renal ADRs include Polyuria, Polydipsia and Acute Lithium intoxication renal effects such as renal insufficiency, acute renal failure, chronic tubulointerstitial renal disease, and NDI. The latter two are discussed here, as these tend to be insidious and are more relevant to safety monitoring, in contrast to the usually acute presentation of Lithium toxicity. Renal safety monitoring is additionally important due to the heightened risks of Lithium toxicity in the presence of impaired renal function. NDI is the most common renal ADR of Lithium therapy with normal or elevated concentrations of the antidiuretic hormone vasopressin. Patients present with polyuria and polydipsia due to a urinary concentrating defect, which can leads to significant volume depletion. The NDI is because of the insensitivity of the collecting ducts to exogenous and endogenous vasopressin, at the level of cellular vasopressin-sensitive adenylate cyclase activity [58]. Experimental studies have shown, that the development of NDI involves chronic treatment with Lithium results in a marked reduction in the vasopressin-regulated water channel aquaporin-2, expressed on the apical plasma membrane of principal cells of the collecting ducts of the nephron and a marked inhibition of water reabsorption, even when serum Lithium levels in therapeutic range [58]. The incidence of NDI among Lithium-treated patients variable in different studies with an estimated prevalence of 20 to 87% [59–61]. Clinically established NDI has been found in about 12% of all patients with Lithium therapy [61, 62]. Many studies have shown, that major risk factors such as duration of treatment, blood Lithium level, dose of Lithium, slow release formulation, clinical non-response and frequency of acute Lithium intoxications affecting the incidence and severity of urinary concentrating defects in Lithium-treated patients, while some other study found that the duration of Lithium treatment and plasma concentrations were not affecting the urinary concentrating defect [63]. A urinary concentrating defect may occur as early as 2 to 4 mo after the commencement of Lithium [6], but it becomes more evident after chronic treatment [64, 65]. NDI may develop even after cessation of Lithium therapy. After 15 y of Lithium treatment, virtually all patients have an irreversibly reduced maximum urinary concentration capacity [64, 66, 67]. On average, the glomerular filtration rates are reduced by–6.22 ml/min over a mean observation time of 1 y, and the urinary concentrating ability reduces by 15% of normal maximum [38]. One study suggests an association between the duration of Lithium treatment and the degree of persistence of hyperkalemia. Because Hyperkalemia could exacerbate Lithium-induced NDI. This ADR clinically very important because patients with Lithium-induced NDI must maintain their oral fluid intake to keep up with their urinary losses to avoid becoming volume-depleted. Because of the risk of volume depletion, some nephrologists recommend treating Lithium-induced NDI to reduce urine volume. One of the treatment options is to reduce Lithium dosage to achieve a serum level of 0.4 to 0.8 mEq/l [6]. By reduce Lithium dosage, it can reduce the polyuria and polydipsia and can be controlled psychiatric symptoms [6]. Another approach is to treat the patient with thiazide diuretics. However, thiazides may cause volume depletion since the patient must consume a sodium-restricted diet for thiazide diuretics to be effective. Thiazides may also cause hypokalemia, and it can exacerbate NDI [6]. One recent case report has shown, that the successful use of indomethacin for the treatment of Lithium-induced polyuria and NDI [25]. However, the long-term use of any NSAID for polyuria has not been tested and may increase serum Lithium levels by decreasing GFR. Amiloride is currently the treatment of choice for Lithium-induced NDI [6]. Amiloride has additional advantages over the conventional treatment of NDI using thiazide diuretics, that it can significantly reduce urine volume when administered chronically to Lithium-treated patients. The action of amiloride on ADH-mediated water transport seems specific in as much as it is capable of reduce Lithium uptake into cells since it blocks Lithium transport by the amiloride-sensitive epithelial sodium channel. In addition, amiloride, by conserving potassium, obviates the need for potassium supplementation that is usually required to prevent hypokalemia when thiazides are used to treat Lithium-induced polyuria.

Interstitial Nephritis is another ADR of a patient treated with Lithium. In several studies in which renal biopsies were performed in Lithium-treated patients, abnormal biopsy results were found that were consistent with chronic interstitial nephritis [6]. These biopsy findings included tubular atrophy and dilation, sclerotic glomeruli, cyst formation, and cortical and medullary fibrosis [6]. The issue of whether Lithium poses a serious risk for chronic interstitial nephritis and renal failure is unresolved. Some studies reports of a Lithium-associated nephrotic syndrome, which is considered as a very rare and reversible ADR. In most of these patients, minimal change disease was observed to have a good prognosis after discontinuation of Lithium. The most important approach is to monitor serum creatinine level of Lithium-treated patients and to maintain serum Lithium level as low as possible to reduce the risk of nephrogenic ADR while controlling the patient's psychiatric symptoms. Renal function must be monitor carefully throughout the course of treatment with Lithium since the development of NDI and chronic interstitial nephritis is often irreversible, even when Lithium therapy is discontinued [68]. Throughout Lithium prophylaxis, it is essential to monitor renal function and Lithium levels at regular intervals, keeping Lithium levels as low as possible and avoiding intoxication.

Cardiac ADRs

Lithium in toxic doses can cause a toxic effect on cardiac. The study has been reported, even at therapeutic doses, Lithium can cause apparently benign and reversible ECG changes consisting of T-wave flattening in patients without pre-existing cardiac disease [69]. Some studies have been reported Lithium can cause the Sinoatrial block in three patients, two of whom had pre-existing cardiac diseases [70–72]. Another patient developed first-degree atrioventricular block on Lithium and trifluoperazine [73]. Another study reports aggravation of ventricular ectopic beats in three of seven patients by Lithium therapy [74].

Cognitive impairments

Cognitive impairment can be distressing for patients and may hamper their compliance to treatment. Several studies have been demonstrated that patients with bipolar disorder have impaired functioning across a range of cognitive domains, even after resolution of mood symptoms, independent of pharmacological treatment [75, 76]. Pharmacotherapy, especially Lithium, has been associated with a poorer cognitive performance [77, 78]. Some study shows, the cognitive function of bipolar patients on Lithium was to be associated with a poorer test performance on tests of memory and motor speed [79], and some comparative study, the cognitive function of bipolar patients on Lithium with controls shows there was no difference in cognitive testing as measured by Bhatia Battery test, PGI memory scale, and Bender Gestalt test [34]. Early studies, who took Lithium themselves, did not indicate any serious disturbances in function, even when the drug was taken at high doses. Another study shows that Lithium therapy had no deleterious effects on cognition [80]. In a study on elderly euthymic bipolar patients treated with Lithium, cognitive impairment on several cognitive domains was demonstrated; however, when other risk factors (age and cardiovascular diseases) were taken into account, Lithium was no longer associated with a poorer cognitive performance [33]. Some studies reported that Lithium treatment was associated with a reduced prevalence of Alzheimer's disease in patients with bipolar disorder [81, 82]. The management of cognitive complaints in bipolar patients is challenging, treatable causes such as clinical or subclinical hypothyroidism should be addressed first. The slowing of cognitive performance can respond well to dose reduction and/or be enhancing thyroid function [83]. Neurocognitive evaluation should be considered in bipolar patients to evaluate the treatment impact on neurocognition [84] better. Patients may benefit from cognitive remediation therapies combined with lifestyle changes. Some well-established strategies within cognitive psychology for memory improvement are as follows: focus attention (free oneself from television and other distractions), elaborate and rehearse information, use of mnemonic devices (for example associate something to remember with an item one is familiar with), and visual concepts.

Sexual adverse effects

Sexual side effects of Lithium can be either primary or secondary [85]. Lithium appears to have minor effects on sexual function. In an earlier study, 14% of bipolar patients on Lithium monotherapy reported a negative effect [86]. The most frequent complaint in men and women is a decreased sexual desire [86–88], although a study on men concluded that the degree of sexual dysfunction was neither a source of distress nor of noncompliance [87]. Specific recommendations to manage Lithium-induced sexual dysfunctions are lacking. A correlation between sexual side effects and serum levels of Lithium could not be demonstrated [86], however, thriving for the lowest effective level is always advisable. Switching to another stabiliser is an option that should be considered with great care. A number of pharmacological agents [cyproheptadine, yohimbine, amantadine, bethanechol, neostigmine, and PDE-5-blockers have been recommended in the treatment of specific dysfunctions, but apart from the PDE-5-blockers, the clinical experience with these drugs in these indications is limited. Physicians and patients should be encouraged to discuss sexual side effects in order to increase compliance and quality of life.

Teratogenic adverse effects

Based on retrospective reports, Lithium is thought to have a high teratogenic risk [89,90]. Although exposure to Lithium in the first trimester does have a 10–20 times greater relative rate of cardiovascular malformations (especially Ebstein's anomaly) compared with the general population, the absolute risk is low (B1 of 1000 infants). The evidence that exposure to Lithium is teratogenic is quite weak, and the risk has been overestimated [38].

Treatment and preventive measures

Psychoeducation should include information on ADRs and their management and should also clarify the general beliefs about medication. Most of the ADRs subside with continued treatment or a temporary reduction of dosage of Lithium. Mood state and serum levels were independently associated with the prevalence and severity of the reported ADRs [52]. Therefore, it is recommended to keep the dose and serum levels as low as clinically possible, without losing efficacy by lowering the dose below the therapeutic range, to prevent ADRs in patients on long-term treatment**.** If general measures are insufficient, specific additional treatment can be offered. Extended-release preparations can reduce tremor. Reducing the use of caffeine and nicotine can have a positive effect. B-blockers and vitamin B6 are effective in reducing tremor [35]. Coated or slow-release tablets appear to be better tolerated. Initial slowly increase dose is the best the option to prevent initial nausea. If nausea occurs, a temporary dose reduction is the best management option, followed by a more gradual increase. Persistent nausea can be treated with the histamine-2 antagonists, famotidine or cimetidine [37]. Dietary counselling and exercise programs is the therapeutic options to reduce weight [91], even before starting Lithium therapy. Switching to CBZ or lamotrigine therapy may be considered if clinically appropriate. In the case of hypothyroidism, up to 2% of Lithium-treated patients require treatment with levothyroxine [50, 51]. Reducing the Lithium level may mitigate NDI or Amiloride at a concentration of 5–20 mg/day is the acute treatment of NDI [92, 93]. Induction of increased potassium levels can be managed with potassium binders such as Sorbisterit. Polyuria can be treated with other medications, such as NSAID, diuretics and amiloride have been shown to relieve Lithium-induced polyuria [12]. Polydipsia is treated as similar to polyuria. The treatment for acne includes topical salicylic acid or tretinoin preparations [94]. Psoriasis in a patient using lithium can be managed with topical steroids, vitamin D analogs, keratolytic, or omega-3 fatty acids [95]. In the case of hair loss, dose reduction or drug discontinuation almost always leads to complete hair regrowth [96].

Therapeutic drug monitoring (TDM)

Lithium has a narrow therapeutic index hence therapeutic drug monitoring (TDM) is necessary. Lithium can cause many ADRs depending on the dose and duration in bipolar disorder. There for Lithium should be started at low dose and titrated to achieve a therapeutic level. The recommended therapeutic range for serum Lithium is 0.4-1.2 Mmol/l on samples taken 12 h after the preceding dose. ADRs and Signs of toxicity often occur when Lithium plasma concentration is greater than 1.5 mmol/l. However, it may occur at therapeutic plasma levels in older people. The usual initial dose of Lithium is 400 mg for adults and 200 mg for older people. The dose of Lithium may gradually increase to 200 mg according to response and ADRs profile. Serum Lithium level less than 1.5 mmol/l-mild toxicity, greater than 1.5 mmol/l-moderate toxicity and greater than 2.0 mmol/l–severe toxicity. Hence, Therapeutic drug monitoring is required when Lithium using in treatment for acute and chronic bipolar disorder.

We have concluded that Lithium has mainstay treatment option for the acute and prophylactic of bipolar disorder. Lithium has the narrow therapeutic index, hence, Lithium can cause many ADRs depending on the dose and duration of the treatment in bipolar disorder. Even at the therapeutic range, 50 to 80% of the patient experience some mild to moderate ADRs, although, some are would be characterised as moderate or severe. The most common ADRs includes polyuria, polydipsia, tremor and weight gain, etc. Other common ADRs Gastric upset include Nausea, Vomiting, Diarrhea, Abdominal Pain, Ataxia, and Dizziness, etc. ADRs are often occurred at in between first week to six weeks at the initiation of Lithium therapy in bipolar disorder when serum Lithium level is rising at the peak levels. Most of the ADRs are often may disappear later next week if persistent, may do better on slow-releasing preparation; alternatively, the dosage of Lithium can be reduced, so that administered more frequent smaller doses. Other ADRs include Hypothyroidism, NDI, Hyperparathyroidism, Dermatological like Acne, Skin rash, Hair loss, Renal Intoxication, Sexual dysfunction, Impaired cognitive state, Cardiac, etc. occurs during the long term Lithium therapy, after six weeks from the initiations of Lithium therapy. Lithium intoxication may occur serum level greater than 2.00 mmol/l. Certain symptoms tend to occur early in treatment

whilst others are of later onset; disturbance of one physiological system may tend to be associated with disturbances in one or more other systems; ADRs of one kind may be of frequent occurrence, whereas others are encountered only rarely. Hence, therapeutic drug monitoring associated with dose and duration of Lithium is required when starting of Lithium treatment in a patient with bipolar disorder.

CONFLICTS OF INTERESTS

There are no conflicts of interest

REFERENCES

1. Tripathi K. Essantial of Medical Pharmacology. 7th ed. New Delhi: Jaypee Brothers Medical; 2013. p. 415.
2. N Bennett MJBP. Clinical Pharmacology. 11th ed. Churchill Livingstone Elsevier; 2012. p. 329.
3. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry 1999;175:336–9.
4. Malhi GS, Tanious M. Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. CNS Drugs 2011;25:289–98.
5. Livingstone C, Rampes H. Lithium: a review of its adverse metabolic effects. J Psychopharmacol 2006;20:347–55.
6. Boton R, Gaviria M, Batlle DC. Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis 1987;10:329–45.
7. Movig KLL, Baumgarten R, Leufkens HGM. Risk factors for the development of lithium-induced polyuria. Br J Psychiatry 2003;182:319–23.
8. Bendz H, Aurell M, Balldin J, Mathé AA, Sjödin I. Kidney damage in long-term lithium patients: a cross-sectional study of patients with 15 y or more on lithium. Nephrol Dial Transplant 1994;9:1250–4.
9. Marples D, Christensen S, Christensen EI, Ottosen PD, Nielsen S. Lithium-induced downregulation of Aquaporin-2 water channel expression in rat kidney medulla. J Clin Invest 1995;95:1838–45.
10. Smith DF BS. Sodium appetite in rats given lithium. Life Sci 1972;11:1021.
11. Weiss NM, Robertson GL. Effect of hypercalcemia and lithium therapy on the osmoregulation of thirst and vasopressin secretion. Vasopressin Raven Press: New York; 1985. p. 281–90.
12. Martin A. Clinical management of lithium-induced polyuria. Ment Hosp 1993;44:427–8.
13. Kosten TR, Forrest JN. Treatment of severe lithium-induced polyuria with amiloride. Am J Psychiatry 1986;143:1563–8.
14. De Wardener HE, Herxheimer A. The effect of a high water intake on the kidney's ability to concentrate the urine in man. 1957. J Am Soc Nephrol 2000;11:980–7.
15. Vendsborg PB, Bech P, Rafaelsen OJ. Lithium treatment and weight gain. Acta Psychiatr Scand 1976;53:139–47.
16. Sachs G. Sanity versus vanity": balancing the problem of weight gain and the benefits of psychotropic drugs. Ther Advan Psychoses 1999;7:842-7.
17. Peselow ED, Dunner DL, Fieve RR, Lautin A. Lithium carbonate and weight gain. J Affect Disord 1980;2:303–10.
18. A Venkoba Rao. A study of side effects of lithium. Indian J Psychiat 1983;25:87–93.
19. Vestergaard P, Licht RW, Brodersen A, Rasmussen NA, Christensen H, Arngrim T, *et al.* Outcome of lithium prophylaxis: a prospective follow-up of affective disorder patients assigned to high and low serum lithium levels. Acta Psychiatr Scand 1998;98:310–5.
20. Becker T. Sex-specific differences in side effects of psychotropic drugs: Genes or gender ? Review Sex-specific differences in side effects of psychotropic drugs: genes or gender? 2016.
21. Teixeira NA, Karniol IG. The influence of age and sex on weight variation in rats treated chronically with lithium chloride. Acta Pharmacol Toxicol (Copenh) 1982;51:1–5.
22. Vestergaard P, Amdisen A, Schou M. Clinically significant side effects of lithium treatment a survey of 237 patients in long-term treatment. Acta Psychiatr Scand 1980;62:193–200.
23. Brady KT. Weight gain associated with psychotropic drugs. South Med J 1989;82:611–7.
24. Vendsborg PB, Rafaelsen OJ. Lithium in man: effect on glucose tolerance and serum electrolytes. Acta Psychiatr Scand 1973;49:601–10.
25. Vendsborg PB, Prytz S. Glucose tolerance and serum lipids in man after long-term lithium administration. Acta Psychiatr Scand 1976;53:64–9.
26. Sussman N, Ginsberg D. Effects of psychotropic drugs on weight. Psychiatr Ann 1999;29:580–94.
27. Biel MG, Peselow E, Mulcare L, Case BG, Fieve R. Continuation versus discontinuation of lithium in recurrent bipolar illness: a naturalistic study. Bipolar Disord 2007;9:435–42.
28. Vm S, Ds M. A longitudinal study of monitoring adverse drug reaction at psychiatric out-patient department in our tertiary care teaching hospital. Surendranagar 2014;4:49–52.
29. Gelenberg AJ JJ. Lithium tremor. J Clin Psychiatry 1995;56:283–7.
30. Johnson G. Lithium-early development, toxicity, and renal function. Neuropsychopharmacology 1998;19:200–5.
31. JK Trivedi, Arunlata PK Dalal, PK Sinha SS. A camparatie study of side-effects of lithium, carbamazepine, and haloperidol in acute mania. Indian J Psychiat 1996;38:248–9.
32. Trivedi JK, Sareen H, Yadav VS, Rai SB. Prescription pattern of mood stabilizers for bipolar disorder at a tertiary health care centre in north India. Indian J Psychiatry 2013;55:131–4.
33. Dols A, Sienaert P, Gerven H Van, Schouws S, Stevens A, Kupka R, *et al.* The prevalence and management of side effects of lithium and anticonvulsants as mood stabilisers in bipolar disorder from a clinical perspective: a review. Int Clin Psychopharmacol 2013;28:287-96.
34. Jefferson JW GJ. Adverse reactions-neurological tremor. Prim Lithium Ther Williams Wilkins; 1977. p. 139–50.
35. Miodownik C, Witztum E, Lerner V. Lithium-induced tremor treated with vitamin B6:a preliminary case series. Int J Psychiatry Med 2002;32:103–8.
36. Bowden CL. Acute and maintenance treatment with mood stabilizers. Int J Neuropsychopharmacol 2003;6:269-75.
37. Stoll AL, Vuckovic A, McElroy SL. Histamine2-receptor antagonists for the treatment of valproate-induced gastrointestinal distress. Ann Clin Psychiatry 2011;3:301-4.
38. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet (London, England) 2012;379:721–8.
39. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: epidemiology and management. Am J Clin Dermatol 2004;5:3–8.
40. Remmer HI, Falk WE. Successful treatment of lithium-induced acne. J Clin Psychiatry 1986;47:48.
41. Pande AC, Max P, Donnelly RF. Lithium-associated with psoriasis. J Clin Psychiatry 1986;47:330.
42. Akkerhuis GW, Nolen WA. Lithium-associated psoriasis and omega-3 fatty acids. Am J Psychiatry 2003;160:1355.
43. Jafferany M. Lithium and skin: dermatologic manifestations of lithium therapy. Int J Dermatol 2008;47:1101–11.
44. McKinney PA, Finkenbine RD, DeVane CL. Alopecia and mood stabilizer therapy. Ann Clin Psychiatry 1996;8:183–5.
45. Mercke Y, Sheng H, Khan T, Lippmann S. Hair loss in psychopharmacology. Ann Clin Psychiatry 2000;12:35–42.
46. Shopsin B. Effects oflithium on thyroid function: a review. Dis Nerv Syst 1970;31:237–44.
47. Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD, *et al.* High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry 2002;51:305–11.
48. Henry C. Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences. J Psychiatry Neurosci 2002;27:104–7.
49. Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. Fifteen-year follow-up of thyroid function in lithium patients. J Endocrinol Invest 2007;30:363–6.
50. Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. J Affect Disord 2005;87:313–7.
51. Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. Clin Pract Epidemiol Ment Health. BioMed Central 2006;2:23.

52. van Melick EJM, Wilting I, Meinders AE, Egberts TCG. Prevalence and determinants of thyroid disorders in elderly patients with affective disorders: lithium and nonlithium patients. Am J Geriatr Psychiatry 2010;18:395–403.
53. Emerson CH, Dyson WL, Utiger RD. Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. J Clin Endocrinol Metab 1973;36:338–46.
54. Lindstedt G, Nilsson LA, Walinder J, Skott A, Ohman R. On the prevalence, diagnosis and management of lithium-induced hypothyroidism in psychiatric patients. Br 1 Psychiat 1977;130:452–8.
55. Villeneuve A, Gautier J, Jus A, Perron D. Effect of lithium on thyroid in man. Lancet 1973;2:502.
56. Transb01 I, Christiansen C, Baastrup Pc. Endocrine effects of lithium. I Hypothyroidism, its prevalence in long-term treated patients. Acta Endocrinol 1978;87:759–67.
57. Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism. J Clin Psychiatry 1999;60:249–55.
58. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. Int J Bipolar Disord 2015;3:28.
59. Okusa Mark D, Luz Jovita T, Crystal M. Clinical manifestations and management of acute lithium intoxication. Am J Med 1994;97:383–9.
60. Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J, Baltimore W, W Lithium. In: Medical Toxicology: Diagnosis and Treatment of Human Poisoning. edited by; 1997. p. 1579.
61. Boton R, Gaviria M BD. Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis. 1987;10:329–45.
62. Movig KLL, Baumgarten R, Leufkens HGM, Van Laarhoven JHM, Egberts ACG. Risk factors for the development of lithium-induced polyuria. Br J Psychiatry. 2003;182(APR.):319–23.
63. Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults--a systematic review. J Geriatr Psychiatry Neurol. 2012;25:51–61.
64. Vestergaard P, Amdisen A. Lithium treatment and kidney function. Acta Psychiatr Scand. 1981 Apr; 63:333–45.
65. Bendz H, Aurell M, Lanke J. A historical cohort study of kidney damage in long-term lithium patients: continued surveillance needed. Eur Psychiatry. 2001 Jun; 16:199–206.
66. Bendz H, Sjodin I, Aurell M. Renal function on and off lithium in patients treated with lithium for 15 y or more. A controlled, prospective lithium-withdrawal study. Nephrol Dial Transplant. 1996 Mar; 11:457–60.
67. Bucht G, Wahlin A. Renal Concentrating Capacity in Long-Term Lithium Treatment and after Withdrawal of Lithium. Acta Med Scand. 2009 Apr; 207(1-6):309–14.
68. TIMMER RT, SANDS JM. Lithium Intoxication. J Am Soc Nephrol. 1999 Mar; 10:666–74.
69. Demers RG, Heninger G. Electrocardiographic changes during lithium therapy. Dis Nerv Syst 1970;31:674–9.
70. Wilson J, Kraus E, Bailas M, Rakita L. Reversible sinus node abnormalities due to lithium carbonate therapy. N Engl J Med 1976;294:1223–4.
71. Eliasen P, Andersen M. Sinoatrical block during lithium treatment. Eur J Cardia I 1975;3:308–11.
72. Wellens H, Cats V, Duren D. Symptomatic sinus node abnormalities following lithium carbonate therapy. Am J Med 1975;59:285–7.
73. Jaffe CM. First-degree atrioventricular block during lithium carbonate treatment. Am J Psychiat 1977;134:88–9.
74. Tilkian AG, Schroeder JS, Kao J, Hultgren H. Effect of lithium on cardiovascular performance: report on extended ambulatory monitoring and exercise testi3ng before and during lithium therapy. Am J Cardia 1976;1:701–8.
75. Martínez-Arán A, Vieta E, Colom F, Torrent C, Reinares M, Goikolea JM, *et al.* Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother Psychosom 2005;74:295–302.
76. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: Epidemiology and management. Vol. 5. American Journal of Clinical Dermatology; 2004. p. 3–8.
77. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000;30:1025–36.
78. Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic Bipolar I Disorder. Psychiatry Res 2001;102:9–20.
79. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. Psychopharmacology (Berl) 2003;170:225–34.
80. López-Jaramillo C, Lopera-Vásquez J, Ospina-Duque J, García J, Gallo A, Cortez V, *et al.* Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. J Clin Psychiatry 2010;71:1055–60.
81. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? Bipolar Disord 2010;12:87–94.
82. Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry 2011;198:351–6.
83. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. Oxford University Press; 2007. p. 1288.
84. Dias VV, Balanzá-Martinez V, Soeiro-de-Souza MG, Moreno RA, Figueira ML, Machado-Vieira R, *et al.* Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. Acta Psychiatr Scand 2012;126:315–31.
85. Demyttenaere K, De Fruyt J, Sienaert P. Psychotropics and sexuality. Int Clin Psychopharmacol 1998; 13 Suppl 6:S35–41.
86. Ghadirian AM, Annable L, Bélanger MC. Lithium, benzodiazepines, and sexual function in bipolar patients. Am J Psychiatry 1992;149:801–5.
87. Aizenberg D, Sigler M, Zemishlany Z, Weizman A. Lithium and male sexual function in affective patients. Clin Neuropharmacol 1996;19:515–9.
88. Zuncheddu C, Carpiniello B. Sexual dysfunctions and bipolar disorder: a study of patients submitted to a long-term lithium treatment. Clin Ther 2006;157:419–24.
89. Nora JJ, Nora AH, Toews WH. Letter: Lithium, Ebstein's anomaly, and other congenital heart defects. Lancet (London, England) 1974;2:594–5.
90. Källén B, Tandberg A. Lithium and pregnancy. A cohort study on manic-depressive women. Acta Psychiatr Scand 1983;68:134–9.
91. Nemeroff CB. Safety of available agents used to treat bipolar disorder. J Clin Psychiatry 2003;64:532–9.
92. Batlle DC, von Riotte AB, Gaviria M, Grupp M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 1985;312:408–14.
93. Bedford JJ, Weggery S, Ellis G, McDonald FJ, Joyce PR, Leader JP, *et al.* Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. Clin J Am Soc Nephrol 2008;3:1324–31.
94. Remmer HI FW. Successful treatment of lithium-induced acne. J Clin Psychiatry 1986;47:48.
95. Akkerhuis GW NW. Lithium-associated psoriasis and omega-3 fatty acids. Am J Psychiatry 2003;160:1355.
96. Mercke Y, Sheng H, Khan T LS. Hair loss in psycho-pharmacology. Ann Clin Psychiatry 2000;12:35–42.

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