Lithium Therapy remains the gold standard in the treatment of bipolar disorder and clinical guidelines recommend it as the first choice for maintenance treatment of bipolar disorder. However, the use of lithium has decreased over the years, mainly due to the fear of its adverse effects. The aim of this paper was to review current literature data for the monitoring and overcoming side effects of lithium therapy in order to provide contemporary evidence for adequate lithium use.

**Material and Methods.** A literature review of lithium therapy in bipolar disorder, using both Medline and manual searches, was performed. Classification of studies, in relation to their quality, was performed using the guidelines established by the American Academy of Neurology. **Results.** Despite methodological limitations of recent studies, there is irrefutable evidence that lithium therapy can cause toxicity and side effects related to renal, thyroid and parathyroid function, as well as weight gain.

**Conclusion.** There is clear evidence that lithium can cause various side effects, but clinically significant conditions in this regard are rare and successfully treated. Literature data confirm strong efficacy of lithium and suggest its wider use in bipolar disorder.

By following clinical recommendations and careful monitoring during lithium treatment, the risk of serious side effects is low compared to its efficacy.

**Key words:** Bipolar Disorder; Lithium; Antimanic Agents; Drug-Related Side Effects and Adverse Reactions; Risk Assessment; Kidney Function Tests; Thyroid Function Tests; Teratogens; Weight Gain; Parathyroid Glands.

**Introduction.**

Mood disorders affect at least 350 million individuals worldwide. They are associated with high morbidity and mortality rate, significant disability, comorbidity with mental and physical disorders, as well as negative social and economic consequences for the patients, their families and the whole society [1, 2]. The cyclical course, as a core feature of bipolar disorder (BD), makes its treatment very challenging. Due to the heterogeneity of symptoms, the treatment of BD is complex and most commonly leads to increase in the number of prescribed medications. The treatment includes a great number of medications, biological therapies (electroconvulsive therapy or transcranial magnetic stimulation) and psychosocial techniques. Treatment tolerability has a significant impact on the long-term management of BD, because adverse effects often lead to treatment noncompliance, which is high. In addition, safety concerns associated with the disease, primarily high risk of suicide, require suitable pharmacological treatment established in the early course of the illness.
Lithium is prescribed all over the world as an effective treatment of depressive as well as manic episodes. Its anti-suicidal action is also proven as very important. Lithium is “the gold standard” among mood stabilizers and all contemporary guidelines recommend it as the first choice in the long-run treatment of BD [3, 4]. Although efficacious, lithium has some clinical disadvantages which include a narrow therapeutic range requiring monitoring of its serum concentrations as well as possible damage to the endocrine and renal systems.

The narrow therapeutic index of lithium salts requires regular monitoring of its serum concentrations and therapeutic actions in case of side effects during a prolonged treatment. Taking into account the decrease in the use of lithium due to the fear of side effects, it is important to obtain clear knowledge on them, in order not to deprive the patients of “the gold standard” in the treatment of BD, and to provide patients with an optimal treatment with maximum efficacy and best tolerability. The absence of side effects leads to a good compliance, and it is a prerequisite for a successful treatment of BD.

Even small deviations in the serum lithium levels may cause clinically significant problems. During prophylaxis therapy, the serum level of lithium under 0.6 mmol/l increases the risk of illness recurrence, and the level above 1.2 mmol/l significantly increases the risk of side effects. This is the main reason why monitoring the serum levels of lithium makes the treatment safe. Lithium ions do not bind to plasma proteins and they do not metabolize. Lithium is almost wholly excreted in the urine, so any changes in renal function, fluid balance or electrolyte levels can potentially lead to lithium accumulation and toxicity [5].

The aim of this paper was to review the current literature on the side effects of lithium during its long-term application in order to determine their frequency, intensity, as well as possible predictors of occurrence.

**Material and Methods**

A literature review of the lithium therapy in BD, using both Medline and manual searches, was performed. Classification of studies, related to their quality, was performed using the guidelines established by the American Academy of Neurology.

**Results**

The use of lithium in the treatment of BD has decreased substantially, partly due to the active marketing of alternative medications, but also because of the perceived risks associated with its use. Side effects of lithium have been in the focus of interest of researchers for years, but the interpretation of the results of decades-long research has largely been made difficult for a number of reasons. In addition to the fact that most studies were methodologically weak, different designs of studies over six decades of research made the combination of data and its synthesis difficult. Thus, the evidence considering side effects of lithium is far from ideal. Despite these limitations, investigators manage to identify five key areas in which lithium therapy produces adverse effects:

1. renal function
2. thyroid function
3. parathyroid function
4. teratogenicity
5. weight gain [6, 7].

The intensity, frequency and possible predictors of the impairment of renal function have remained insufficiently clarified [8]. The renal side-effects are of greatest concern to both clinicians and patients, and in this regard the analysis is reassuring: even with long-term lithium use, the risk of renal toxicity, specifically end-stage renal failure, is fairly low (0.53% compared to 0.2% in the general population). Chronic kidney disease is more common, but it occurs predominantly at older age and only in a small proportion of this group (2%) it progresses to end-stage renal failure. New studies identified predictors for a decline in renal function: female gender, age, comorbidities such as diabetes mellitus or hypertension, and high median serum lithium concentration. The length of lithium treatment has a negative association with side effects which suggests that the effects have rapid onset once patients start taking lithium [6, 8, 9]. The identification of the potential causal effect of lithium on renal function is difficult, because of the confounding effects of diabetes and cardiovascular disease, which may lead to decline in renal function. The literature data suggest that stable lithium maintenance therapy does not increase the risk of renal dysfunction in adult patients with affective disorders who have a baseline glomerular filtration higher than 60 ml/min. These results therefore contradict the opinion that long-term lithium therapy is associated with nephrotoxicity in the absence of episodes of acute intoxication and that duration of therapy and cumulative dose are the major determinants for toxicity [6]. If there is a decrease in renal function in patients treated with lithium, contemporary guidelines focus on active management of diabetes, hypertension and other cardiovascular risk factors, avoidance of episodes of acute lithium toxicity, dehydration and other drugs that can reduce renal clearance of lithium [10–12]. Structural changes may occur in the glomerules of lithium-treated patients, but they are nonspecific and can be seen also in patients before the start of lithium treatment. The morphological changes that are specifically associated with lithium therapy are confined to the distal tubules and collecting ducts and are reversible.

**Abbreviations**

- BD – bipolar disorder
- TSH – thyrotropin-stimulating hormone
- T4 – thyroxine
[13]. The results of newer studies are encouraging because they suggest that lithium treatment is not nephrotoxic. However, substantial uncertainty remains because most of these studies were of short duration and unable to detect long-term effects. Present clinical recommendations include assessment of renal function before the beginning of lithium therapy and henceforth monitoring at intervals as short as 6 weeks. Because the absolute risk of end-stage renal failure is so low, annual testing is probably sufficient in the absence of clinical reasons for more frequent monitoring [8].

Lithium has four negative effects on thyroid function, which include inhibition of iodine uptake, inhibition of triiodothyronine (T3) secretion, alteration in thyroglobulin structure, and inhibition of thyroxine (T4) secretion. Recent studies have shown that in lithium-treated patients there is a significant rise in mean serum thyrotropin-stimulating hormone (TSH) and a significant fall in mean serum T4, 6–12 months after the start of lithium treatment. The TSH concentrations tend to increase in response to the inhibitory effect on T4 availability. Similarly to the development of renal side effects, the risk of hypothyroidism seemed to be greatest at early stages of lithium treatment (6–12 months after initiation). Reports about the incidence of this side effect range from 1% to 30%, and almost all hypothyroid patients respond to supplementary treatment with T4 [9, 13]. This side effect can be successfully treated and it does not represent a contraindication for lithium use. Risk factors for development of hypothyroidism in patients receiving lithium therapy include female gender, young age, old age, patients with diabetes and high median serum lithium concentration. Most of these patients are asymptomatic and the diagnosis is made only biochemically. It is unclear when subclinical hypothyroidism needs intervention, especially given the complex interaction between thyroid status and mood. As the symptoms of lithium-induced hypothyroidism overlap with those of depression, the underlying cause may remain undiagnosed and untreated by psychiatrists. Determination of serum TSH, a sensitive indicator of decreased thyroid function, may help resolving diagnostic doubts [8, 9]. Although with a far lower incidence, an increased risk of hyperthyroidism may be seen in patients treated with lithium [14].

There is a positive association between lithium and hyperparathyroidism. Primary hyperparathyroidism is quite frequent in patients receiving lithium: an absolute risk of 10% (vs. 0.1% in the general population) is probably attributable to lithium’s inactivation of the calcium-sensing receptor and interference with intracellular second messenger signaling. This effect leads to an increased release of parathyroid hormone, which raises calcium concentrations in blood. Thyroid and parathyroid abnormalities occur in about 25% of patients receiving lithium therapy and that is why close clinical monitoring should be done. More research is needed to clarify the relation between lithium, calcium and kidney function [6, 8, 9]. Guidelines for BD make no mention of serum calcium level monitoring, which seems to be an important omission in view of the high absolute risk of hyperparathyroidism. Baseline blood tests before lithium is introduced should include TSH and serum calcium, and these tests should be repeated every year or more frequently if clinical symptoms are reported [9, 15].

Maternal physiological changes during pregnancy may necessitate drug dosage adjustments. For example, the glomerular filtration rate increases during pregnancy causing many medications to be excreted more rapidly. As a result, serum concentrations may fall and the patient may require higher doses to prevent relapse. Serum lithium levels should be maintained in the therapeutic range during pregnancy. After establishing the pre-pregnancy baseline, lithium levels should be checked monthly during pregnancy, unless it is clinically indicated to do so more often. Lithium dose usually needs to be increased over the course of pregnancy. It is recommended to check lithium levels on weekly basis in the last month of pregnancy, both because of increased clearance rates and because of the potential toxicity of lithium in complications such as pre-eclampsia. Dosage of lithium needs to be reduced one week before delivery. Clearance and fluid volume decreases after the delivery which can lead to higher serum lithium concentrations and side effects unless dose is reduced. Lithium serum level should be checked 24 hours after the delivery and after each dose adjustment [16, 17].

The association between lithium exposure and Ebstein’s anomaly has been established earlier and previous analysis of the published data estimated the risk to be 1 to 2/1000 live births. Recent analysis suggests that exposure to lithium in the first trimester is actually associated with a 0.05–0.1% risk of cardiovascular anomalies (a low absolute risk, but perhaps still higher than in the general population). High-resolution ultrasound and fetal echocardiography are recommended based on the possibility that lithium increases risk of heart defects [6, 18]. The evidence that exposure to lithium is teratogenic is quite weak and authors suggested that the risk has been overestimated. However, studies have never been large enough to be decisive. Adequate control of the mood disorder is of paramount importance in order to provide the greatest benefit to the mother and child while minimizing potential risks. Clinicians should explain the uncertainty of risk to women of childbearing age considering the balance of risks between possible harm to the baby and maternal mood instability before continuation or stopping lithium therapy [9, 17, 18].

There is a positive association between lithium and weight gain and factors which may explain it are its insulin-like properties in increasing cellular glucose uptake, increased thirst, direct stimulation of the hypothalamic appetite centre, and the induction of hypothyroidism. Risk of increased weight
gain and body mass index is quite lower with lithium compared to atypical antipsychotics and other mood stabilizers [9, 19]. The increase in body weight may impair the compliance and the doctor–patient relationship and also lead to a number of other medical complications, such as high blood pressure, high triglycerides and diabetes [20].

When initiating lithium therapy, prescribers should advise the patient that poor adherence or rapid discontinuation may increase the risk of relapse, discuss lithium’s side effects, monitor patient’s weight, serum urea, electrolytes, creatinine, thyroid hormones, and rule out pregnancy. After starting the treatment, serum levels of lithium should be between 0.6 – 0.8 mmol/L. The optimal maintenance level is the highest dose tolerated without significant side effects and will vary from patient to patient. Lower levels may be required in the elderly, as they may experience toxicity at standard therapeutic blood levels [11, 12, 21].

Monitoring lithium:
1. Check serum lithium levels routinely every 3 months
2. Consider measuring serum lithium levels even more frequently for:
   - Older people
   - People taking drugs that interact with lithium (thiazides, nonsteroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors)
   - People at risk of renal, thyroid or other complications
   - People with poor symptom control
   - People with poor adherence
3. Other indications for checking serum lithium levels include:
   - Clinical deterioration
   - Abnormal laboratory results
   - Change in sodium or fluid intake
   - Symptoms suggestive of abnormal renal or thyroid function
4. At every appointment check patients for symptoms of neurotoxicity (tremor, paresthesia, ataxia, cognitive impairment) which can occur at therapeutic levels, and gastrointestinal symptoms (anorexia, nausea, diarrhea) which can be signs of lithium toxicity.
5. When discussing whether to continue lithium, take into account clinical efficacy and other risk factors for renal impairment [11, 12, 22].

Conclusion

The use of lithium has decreased all over the world, mostly due to the fear of side effects. The evidence of recent studies indicate that the use of lithium should increase again, because there is no threat of more serious side effects if clinicians respect recommendations and conduct close monitoring during treatment.

Studies have shown that lithium therapy is associated with increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism and weight gain. Most of the studies showed no significantly increased risk of congenital malformations, alopecia or skin disorders and little evidence for a clinically significant reduction in renal function in most patients. The evidence that lithium can adversely affect the endocrine system is clear, but clinically significant conditions are either rare or treatable. Due to the fact that higher mean serum lithium level has been identified as a risk factor for all lithium side effects, prescribing lithium within the reference range is particularly important. Findings suggest that close monitoring of adverse effects in all patients taking lithium is essential, and that clinicians should do their best to use the lowest effective dose of lithium. Timely diagnosis and treatment of associated medical conditions (diabetes, hypertension and other somatic diseases which are more common in patients suffering from bipolar disorder than in general population) is equally important. Extra effort is required to follow the guidelines and precautions that ensure maximum efficacy and safety of lithium treatment because our patients are entitled to it.

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