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When and how to use Lithium

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ABSTRACT

Background: Lithium is an old proven medication, but it is infrequently used in current practice. This review examines evidence for its benefits and risks, and provides clinical guidance to its use. **Methods**: Narrative review. **Results**: Besides its benefit in bipolar illness, lithium has important underappreciated proven benefits in prevention of unipolar depression and suicide. Emerging data support neurobiological benefits for cognition and possible dementia prevention. Likely benefits also exist in low doses for mood temperaments (cyclothymia and hyperthymia). High doses (over 1.0 mmol/L) should be avoided since they increase side effects, complications associated with long term use, and risk of toxicity. Conversely, low dosing can be legitimate, especially for suicide and dementia prevention. Nuisance side effects of lithium may affect adherence, and medically serious side effects can occur. Managing strategies are available for side effects. **Conclusion**: Lithium is the most effective medication in psychiatry, because it has disease-modifying, not just symptomatic, effects. It is effective not only for bipolar illness but for prevention of suicide, episodes of unipolar depression, mood temperaments, and possibly dementia. Its many benefits need better appreciation, while lowered dosing can reduce risks.

Clinical Recommendations

- Lithium efficacy, especially for suicide and dementia, can be present at lower therapeutic levels than traditionally recommended.
- Prevention of unipolar depression is an underappreciated proven benefit of lithium
- Low dose lithium levels likely are effective for mood temperaments of cyclothymia and hyperthymia
- Chronic renal side effects occur in 1-5% of patients with decades of treatment, a lower rate than commonly believed.

- Lithium should be dosed only once daily, which reduces long-term kidney risks.
- Titration should be to clinical efficacy, not blood levels.

Limitations:

- Proof or disproof of lithium efficacy in dementia prevention requires more randomized clinical trial data
- Nuisance side effects can prevent lithium use in some persons

Keywords: lithium, bipolar illness, depression, dementia, suicide, side effects, dosing

INTRODUCTION

Lithium may be the most effective medication in psychiatry: Its effects are not merely symptomatic, as with most psychotropic drugs, but rather disease-modifying (prevention of mood episodes and improved long-term course of illness, prevention of suicide, reduction of mortality) (1). Unlike most psychotropic drugs, lithium's benefits increase with time (2). Long-term recovery, not immediate short-term acute improvement, is its strength (1,3–5).

Knowing when and how to prescribe lithium, is essential for practicing clinicians. Unfortunately, many clinicians, especially of younger generations, have little experience with prescribing lithium, and avoid it unnecessarily (4), partly under commercial influence for newer patented drugs (6,7). Its side effects and potential harms are well-known, of course, and also need to be taken into account.

Clinical indications for lithium are not limited to bipolar illness (8). In fact, when lithium was first studied in the 1950s and 1960s, and shown to be effective in manic-depressive illness (MDI) (6,7), the latter condition was defined as meaning unipolar depressive illness (i.e, only depressive episodes) *or* bipolar illness (i.e., manic and depressive episodes). Kraepelin's concept of MDI meant manic *or* depressive episodes, not manic *and* depressive episodes. Thus, it included both bipolar and unipolar depressive types of mood illness. Subsequently the DSM-III combined unipolar depression with other depressive clinical pictures, under the broad concept of "major depressive disorder". Hence, from the very beginning, lithium was studied in, and proven effective for, unipolar depression, not just bipolar illness (7).

We suggest there are five main clinical indications for lithium treatment: *bipolar illness, unipolar depression, suicide prevention, mood temperaments, and dementia prevention*. Of these, only the first indication in bipolar illness is widely known; this review will emphasize the other four.

In the present review we will examine the main clinical indications for lithium for prevention and treatment of psychiatric conditions, along with addressing dosing considerations, and nuisance and serious side effects.

Clinical Indications

Clinical indications for lithium are described in Table 1 and overall guidance summarizing each section of this paper are provided there. Four major categories are reviewed: bipolar illness, unipolar depression, suicide prevention, and dementia prevention.

Bipolar illness

Lithium is effective in the treatment of acute mania (9). It has a slower onset of action as antipsychotics (6 to 10 days vs. 2 to 6 days) but achieves similar remission rates (10–12). It also is effective in the treatment of acute bipolar depression (13). The main strength of lithium is in preventing new mood episodes, where it may be even more effective at prevention of depression than manic states, as shown in the BALANCE study (14).

The appropriate level of lithium for type II bipolar illness is not established (13). Levels based on acute mania studies are not necessarily relevant to type II bipolar depression populations. It is our general practice and viewpoint that lower levels can be sufficient, and clinicians should be flexible to allow for possible efficacy at lower levels, in the 0.4-0.8 mmol/L range (12,15–18). Other recent reviews on this indication are available (19–21).

Prevention of unipolar depression

Some clinicians are skeptical about the effectiveness of lithium in unipolar depression (22,23), but a recent metanalysis of 39 randomized clinical trials (23) supports such efficacy. Lithium was superior to placebo as an augmentation agent (odds ratio, OR 2.5; number need to treat, NNT 4.9), and superior to placebo for treatment-resistant depression (OR 3.1). As a prophylactic strategy, at 12 to 36 months, lithium alone was more effective than placebo (RR = 4.5, NNT 2.8), and to tricyclic antidepressants (OR 2.2). Lithium also was more effective added to tricyclic antidepressants versus tricyclic antidepressants plus placebo (OR 2.4).

Although this meta-analysis focused on earlier studies comparing tricyclic antidepressants, there is no logical reason to doubt similar results with newer antidepressants, especially since tricyclic antidepressants are, if anything, more effective than serotonin reuptake inhibitors (SRIs) and other new antidepressants (24). These considerations become especially relevant to the use of lithium in

prevention, or maintenance, of unipolar depression. The current extensive literature on SRIs and other modern antidepressants (over 500 randomized trials) indicates that these agents are modestly effective acutely, short-term, for clinical depressive episodes (24). Their efficacy in prevention of depressive episodes is much less well proven (15 randomized trials) (25), and is questionable based on the potential invalidity of the "enriched" randomized discontinuation (26). If these concerns are valid, then lithium may be a more proven and more effective treatment for prevention of depressive episodes in unipolar mood illness. The clinical approach then would be to use SRIs or other modern antidepressants short-term for the acute depressive episode, i.e., for about 3-6 months, and then to switch to lithium for long-term prevention.

Some studies have suggested that low levels are less effective than standard levels for unipolar depression, but the literature is not definitive (27). In the latter metanalysis average lithium levels were 0.79 mmol/L. We recommend dosing to clinical effect, and only if patients do not respond to low levels (0.4-0.6 mmol/L) would it be necessary to increase to the standard levels above (12). Again, long-term maintenance levels are not proven to be the same as acute levels, thus clinical flexibility is reasonable, with openness to lower levels long-term than acutely.

Suicide prevention

It is important to realize that *lithium is the only medication ever proven to prevent suicide in double-blind placebo-controlled randomized clinical trials* (28,29). Meta-analysis of four placebo-controlled lithium trials showed 87% decreased risk of suicide (odds ratio 0.13) (29), which means that only about one in ten persons committed suicide who would have committed suicide without lithium. (There were zero suicides in the lithium arm versus six suicides in the placebo arm). Contrast this large effect size with the modest statistically non-significant 15% decrease in suicidality (not completed suicide) with SRIs (30). Since only about 5-10% of persons who make suicide attempts eventually commit suicide, the antidepressant benefit for completed suicide is not more than about 1% at best. This contrasts with 87% with lithium. In other words, lithium is about 90 times more powerful in prevention of suicide than antidepressants. Or, put another way, for every one person whose suicide is prevented with antidepressants, lithium would prevent suicide in 90 persons. Consequently, for suicide prevention, these randomized studies of lithium and of antidepressants demonstrate that using

lithium more widely and using antidepressants less would be more consistent with our best scientific evidence (31,32).

Lithium also generally had less suicide rates than most active comparators, including other agents known to be effective in bipolar illness, like carbamazepine (29). Other studies have compared lithium and valproate, and again lithium seems to have a preferential anti-suicide effect in bipolar illness, while suicide rates are not decreased by valproate (33).

The benefit seen with lithium was present also in unipolar depression, with a 64% decreased suicide risk, and an 87% of decreased number of total deaths, compared with placebo (29). As well, in the long term the use of lithium is linked to 44% reduced suicide risk, as shown in large cohort studies (34).

On the other hand, parasuicidal self-harm was not affected by lithium (29).

Geological studies

Since lithium is as mineral found in rocks, it seeps into the soil and is taken up by plants, which are eaten by animals. Hence, lithium is found in the normal human diet, usually at about 1 mg/d elemental lithium. Some foods, like eggs, are high in lithium. Typically, though, the amount of lithium in the diet is dependent on the influence of a region's water supply on foods. Some areas of the US have more lithium in the water than others, and so too with different parts of the world. This distribution of lithium has led to numerous geological studies examining the association between lithium in the water and behavioral outcomes, especially suicide, as well as medical outcomes and mortality. Such studies have been conducted over the past fifty years. Being observational, they all share the weakness of all epidemiological research: correlation may not reflect causation.

In the case of suicide, though, we now have randomized data of efficacy with lithium, as shown above. Hence the observational data on that topic is more likely to be valid.

In a summary of that literature (35), nine of eleven epidemiological studies, usually of drinking water sources, found an association between high amounts of lithium and beneficial behavioral and medical outcomes. Sample sizes were often large (5 million in one study, 8 million in another), including regions such as over two dozen Texas counties, the entire state of North Carolina, the 100 largest American cities, 99 districts in Austria, and provinces in Japan and Chile. In all cases,

water levels were tested for lithium availability. Outcomes assessed were major behavioral abnormalities, (like suicide, homicide, psychiatric admissions, crimes), some medical illnesses (like cardiovascular disease), or overall mortality. Suicide, the most commonly measured outcome, was reduced in four of five studies.

The studies included in the metanalysis of randomized studies of lithium in mood illnesses tended to use standard doses. Yet the extensive geological literature on lithium suggests efficacy for suicide prevention at much lower doses (36,37). "High" means about 1-2 mg/d of elemental lithium (compared to standard doses of around 900 mg/d lithium carbonate, equivalent to about 170 mg/d of elemental lithium). Even at these very low doses (1-2 mg/d), the lithium in the water studies showed notable evidence of decreased suicide rates associated with "high" lithium in the water, compared to other regions with low or no lithium (38–42). These observational studies could be affected by confounding factors (43), though some, like urban versus rural location and socioeconomic status, were addressed (37,38,40).

In short, lithium may prevent suicide even at very low doses, as low as 1-2 mg/d of elemental lithium (equivalent to 5-10 mg/d of lithium carbonate). Concerns about side effects and toxicity, discussed below, relate to much higher doses (usually about 900 mg/d), that are over 100-fold higher than these very low doses.

A final relevant feature of these geological studies is that they are generalizable to the general population, not only patients with diagnosed mood illnesses. Hence low levels of lithium in particular may be relevant to persons without mood illnesses, such as individuals at risk for dementia or persons with suicidality who have non-mood illness diagnoses (such as post-traumatic stress disorder).

Dementia prevention

There is a 2-3 fold increased risk of dementia in persons with severe mood unipolar depression or bipolar illness (44–46), likely associated with the excitotoxic effects of steroid activity which is increased with depression and mania (46). This risk is removed with lithium treatment, but not with other psychotropic medications. In a 30 year prospective study from Zurich, lithium-treated patients with mood illnesses did not have increased risk of dementia, unlike non-lithium treated patients (47).

The Zurich study has been confirmed by the majority of other studies. Five out of seven epidemiological studies have found an association between standard dose lithium and low dementia rates (35).

The first geological study of the topic supports the clinical lithium studies. In a national study in Denmark (48), with a mean age studied of about 80 years, dementia rates were lower in regions with higher lithium exposure in the water. Compared to low lithium levels of less than 5 mcg/L, if lithium levels were above 15 mcg/L, dementia risk was decreased by 17%.

Four randomized clinical trials (6-15 months in duration) have now been conducted on lithium for Alzheimer's dementia, and all have found some clinical or biological benefits versus placebo, though small samples and short follow-up limited statistical power (35). One study used very low dose lithium of 300 µg daily for mild Alzheimer's dementia, showing no further worsening on the Mini-Mental State examination over 15 months of treatment, compared to notable worsening in the placebo group (relative risk 2.0, 95% confidence intervals 0.64-6.20).

Further, mood illnesses are often associated with cognitive symptoms, which may improve when mood improves, or may persist (49). Lithium plausibly could improve such cognition, given the extensive evidence that lithium has neuroprotective and neurotrophic effects (11,50).

In sum, the above evidence suggests that lithium's proven biological neuroprotective benefits may translate to clinical benefits for cognition and possibly dementia prevention. Given the high rates of dementia in mood conditions, the use of at least very low dose lithium for long-term dementia prevention would be plausible.

Other Clinical Features

Rapid-cycling and other poor prognostic groups

It has been demonstrated that lithium response is lower in patients with rapid-cycling (51), psychotic features (52), or substance abuse (53) (compared to not having those states). However, those clinical pictures are generally treatment-refractory, and, contrary to common opinion, anticonvulsants have not been shown to be more effective than lithium in those states (51–53). The

only condition in which anticonvulsants have clearly been shown to be more effective than lithium is in the acute mixed episode (54).

Older persons

It is not appreciated by many clinicians that lithium doses should be reduced in older persons (55). The blood-brain barrier becomes more porous with age, such that by age 70 or above, lithium crosses it easily. In younger or middle adulthood, lithium levels in the brain are about half that seen in the blood. A sodium-potassium pump at the blood-brain barrier actively pumps lithium out of the cerebrospinal fluid. Thus, a blood level of 0.8 mmol/L corresponds to a brain level of about 0.4 mmol/L. However, by age 70 or later, the blood and brain levels are similar, such that a blood level of 0.4 mmol/L is therapeutic, equivalent to a level of about 0.8 mmol/L in younger persons. In contrast, a blood level of 0.8 mmol/L in an older person above age 70 can be equivalent to toxic level of about 1.6 mmol/L in younger persons.

Blood levels of lithium in older persons need to be about half the level used in younger persons. This fact may not be only due to increased blood-brain barrier permeability, but also due to changes in membrane transport with resulting higher intra/extra cellular ratio of concentrations. Unfortunately, laboratories do not correct for age, and incorrectly report that levels are "therapeutic", when they are toxic, and "subtherapeutic", when they are therapeutic, in older persons. In general, it is best to keep lithium levels very low, i.e. 0.4 mmol/L or lower, in older persons, even when using them for standard mood episode benefits. Levels should not exceed 0.6 mmol/L in older persons.

Mood temperaments

Another scenario where low lithium levels may be effective is the treatment of mood temperaments, i.e., cyclothymia and hyperthymia. Unfortunately, these conditions are not studied much because they are not prominent in the DSM system of diagnosis. There are no randomized studies, and available discussion is observational or limited to clinical experience (56). With that limitation, available clinical experience supports effectiveness of low doses of lithium in cyclothymia or hyperthymia, in our experience, about half the doses (300-600 mg/d) and levels (0.4-0.6 mmol/L) used for standard bipolar illness.

Lithium withdrawal syndrome

It is important to recognize that lithium should not be abruptly discontinued (except in a medically dangerous case of acute lithium toxicity). If stopped suddenly, there is a 50% risk of sudden mania within one month (57), as well as some evidence of a marked increased short-term risk of suicide (58,59). If tapered over two weeks or longer, those risks appear to subside (60). Thus, lithium should generally be tapered at that speed; often a reduction of 300 mg per week is sufficient, or lowering the dose by about 25% every two weeks (7).

Stigma and other concerns

Despite the many clinical benefits of lithium, clinicians often remain hesitant to prescribe lithium. Older clinicians may have had bad experiences in the past, when, in the absence of viable alternatives, lithium was dosed at high levels. Younger clinicians simply are unfamiliar with it (1,4).

Dr. Frederick Goodwin, former head of the National Institute of Mental Health and a key lithium researcher in the 1960s and 1970s, once expressed the view that "if you can't or won't use lithium, get out of the business of treating bipolar disorder" (SN Ghaemi, personal communication, 2020). Another way of expressing this is idea is that, all other things being equal, for the average person with bipolar illness, one need not find reasons to prescribe lithium; one needs reasons *not* to prescribe it.

Some clinicians worry that patients might overdose on lithium, but if it prevents suicide, then this risk is mitigated. In other words, patients are less likely to overdose if they are given lithium than not.

Sometimes the doctor is willing, but the patient is not. Often this reluctance has to do with the fact that lithium has long been associated with the diagnosis of manic-depressive illness, and thus may carry more stigma than newer drugs (7,61). In other cases, patients may have taken lithium in the past, often in the hospital, with many side effects. The latter scenario often involves high blood levels of lithium combined with polypharmacy with antipsychotics or other agents. Patients may not have side effects with lithium alone, especially if titrated

very gradually (13).

Patients need to be educated: Choice of medication does not increase or decrease the severity of an illness. If clinicians describe the whole range of benefits of lithium, especially for mortality and cognition, patients are more willing to take it. Likewise, for those patients especially attracted to natural treatments, like herbal medications, clinicians should explain that lithium is a mineral, not a synthetic chemical, and indeed is the third element, after hydrogen and helium, in the table of chemical elements.

Mechanism of action

Most psychotropic agents are "first messengers", having their action at the synaptic level. Further changes inside the affected neurons are indirect. Lithium, valproate and carbamazepine bypass the synapse, and directly affect these "second messengers" inside neurons. Of these agents, while it also has some effects on the synapse (such as mild serotonergic agonism) (62), lithium has the most extensive "second messenger" effects. It stimulates some G-proteins and blocks others; it inhibits protein kinase C and the phosphatidylinositol phosphate cascade (63). It also inhibits glycogen synthase kinase-3 (GSK-3), lowers tau protein levels, and inhibits tau phosphorylation and aggregation (64). The latter two effects are important mechanisms related to lithium's potential benefits in dementia prevention. It has a range of effects, which end in affecting gene expression in the nucleus of the axonal neuron. Those genes then change what neurotransmitters they produce and change the physiology of the neuron, modifying projections and connections with other neurons. This is a very slow process, but the end-result is a change in microanatomy of the brain, and overall neuroprotective effects.

Dosing

Lithium levels

Proposed target levels are described on Table 2. The usual dosage of lithium carbonate is around 900 mg/d (range 600-1200 mg/d). It is dosed to a serum therapeutic range of 0.6-1.0 mmol/L, and somewhat lower in the elderly (0.4-0.6 mmol/L). Early studies described a benefit from lithium

from 0.5 to 0.8 mmol/L (65). Currently, a typical level for acute and maintenance treatment is 0.8 mmol/L (13,66) (0.4 in the elderly) (19,67). However, maintenance studies suggest similar results in the 0.6 to 0.8 mmol/L range. No studies show more benefit above 0.8 mmol/L, thus higher levels should be avoided at maintenance, certainly above 1.0 mmol/L. There is no clinical efficacy rationale for such higher levels, and the risk of toxicity increases as one gets closer to the borderline toxic range of 1.2-1.5 mmol/L, with minimal side effects of tremor, nausea, diarrhea, and ataxia. Levels from 1.5-2.0 mmol/L are associated with a higher risk of seizures (68). Above 2.0 mmol/L, acute renal failure can occur, and dialysis may be warranted. Above 2.5 mmol/L, coma and death can occur, and dialysis is indicated (69). In the elderly, these signs of toxicity can occur at half the levels (67). As noted above, a special warning is appropriate for older persons, especially those with depression in whom decreased food and liquid intake can raise lithium levels to toxic ranges quickly. If renal failure occurs, lithium levels rise exponentially, making dialysis essential (69).

Lithium is not metabolized in the liver and is excreted unchanged by the kidney. Thus, its only drug interactions involve other medications that can affects its renal excretion.

Dosing titration

Like most medications, lithium should be dosed to clinical efficacy, not blood level. This is a common clinical error. A lithium level is not "subtherapeutic" if the patient is responding to it clinically.

In general, a very slow titration of lithium is wise, because it limits side effects and allows for efficacy at lower doses than are commonly used. An exception for this titration is that if someone is markedly symptomatic with severe depression and/or mania, and the clinician has other reason to believe they will tolerate lithium (such as past use without side effects); in that case, a more rapid titration to standard levels is reasonable. Outside of those circumstances, a slower titration such as the following may be suggested. Begin lithium 300 mg qHS for 2-3 weeks; if insufficiently effective, increase to 450 mg qHS for 2-3 weeks; if insufficiently effective, increase to 600 mg qHS for 3-4 weeks; if tolerated but insufficiently effective increase to a full dose of 900 mg qHS and check a level with a goal of 0.8 mmol/L at that dose. If the patient begins to improve at lower doses, leave lithium at the lowest effective dose and check the lithium level only for documentation. Steady state lithium

levels should be determined after 5-6 half-life periods, that is after 5-6 days after completing titration. Since the time to steady state increases in elderly patients and in those with impaired renal function, the lithium level should be measured again after 10-12 days (19). In subjects in remission, dosing to levels may be appropriate since clinical symptoms are not present.

Dosing frequency

Lithium should only be dosed once daily since it has a mean half-life of 24 hours (21) and increases over time up to 58 hours after 1 year of therapy. Once daily dose improves compliance and reduces renal toxicity (70,71). The common practice of dosing lithium multiple times daily is based on habit without any general rationale. However, in some cases, if adverse effects are associated to a single dose posology, changing to more than once daily dosing may reverse them. Dosing lithium at night minimizes sedation and other adverse effects associated to the blood peak (Cmax). Another option is to use extended or slow release lithium (like generic lithium carbonate ER or various trade alternatives). These formulations induce a lower blood peak and a slower increase in serum lithium concentrations, all of which may reduce incidence and severity of side effects, including tremor, gastrointestinal symptoms (i.e nausea, upper gastrointestinal cramping), rash, cognitive dulling, urinary frequency and neuromuscular slowing (72,73). Slow release formulations may also lead to somewhat less impairment of urinary concentration capacity (70). The liquid formulation of lithium citrate also may reduce gastrointestinal side effects.

Very low dosing can be legitimate

As described previously, geological studies of lithium show benefit for suicide prevention, mortality, and possibly dementia prevention at very low doses that are equivalent to about 1-5 mg/d of elemental lithium. While this section may be seen by conservative clinicians as speculative, it is supported by the geological data provided previously in this paper. In the normal diet, we consume about 1 mg/d of elemental lithium. In the water studies, "high" amounts of lithium meant more than that amount. Thus, about 5 mg/d of elemental lithium would be considered high by dietary standards (74). These very low doses are difficult to obtain with standard pharmacological formulations of

lithium. With lithium carbonate, for instance, 100 mg/d of that compound is equivalent to 18.8 mg/d of elemental lithium. The "standard" lithium dose of 900 mg/d of lithium carbonate translates to about 170 mg/d of elemental lithium, which is extremely high, using the standards of naturally consumed lithium. So a "high" dietary amount of 5 mg/d of elemental lithium would translate to about 25 mg/d of lithium carbonate. In some countries, lithium carbonate is available in pill form in a dose of 150 mg/d at the lowest. Thus, very low dose lithium could be given only if about one-quarter of a pill (37.5 mg/d) was given every other day, or if half a pill (75 mg) was taken two to three times weekly. Another alternative would be to use liquid lithium citrate, which is dosed at 300 mg per 5 ml, so that 0.5 ml would be 30 mg. Over the counter formulations of lithium in the United States are made to provide 5 mg/d of elemental lithium in one pill, either as lithium orotate (120 mg) or lithium aspartate. These over-the-counter are reasonable alternative to prescribed lithium if the drug is being used at very low dose for dementia prevention mainly. For suicide prevention in patients with mood illnesses, it may be more effective to use standard lithium carbonate pills, even if only lower doses (such as 150-300 mg/d) are used. In patients with diagnosed mood conditions, higher doses of course can be used if tolerated, whether for mood or suicide prevention. The point here is that very low dose options also may legitimate in patients without mood diagnoses, especially for dementia prevention.

In other words, if the geological studies of lithium are correct, clinicians may be justified in rethinking their conception of lithium dosing and coming to the conclusion that there is almost no minimum to lithium dosing. At very low doses, any amount of lithium is better than none, at least for dementia and suicide prevention.

Side effects

It is useful to divide risks into two major groups: nuisance and medically serious harms. Among the latter, the most important are kidney and thyroid effects.

Nuisance side effects

Nuisance side effects occur at therapeutic levels, are experienced as troublesome, and are often related to noncompliance (61,75). These include sedation, cognitive difficulties like poor concentration and memory, a sense of decreased creativity, dry mouth, hand tremor, increased appetite, weight gain, increased fluid intake (polydipsia), increased urination (polyuria), nausea, diarrhea, psoriasis, and acne (76). Polydipsia and polyuria persist in about 25% of patients during maintenance treatment with lithium. Duration of treatment, higher serum lithium levels, episodes of lithium intoxication and the ingestion of other psychotropic medications, especially antipsychotics, are proposed risk factors (76,77). When severe, this increased urination may represent nephrogenic diabetes insipidus, a condition due to lithium's inhibition of the kidney's sensitivity to the pituitary's antidiuretic hormone (ADH, or vasopressin) (78).

Some of these side effects are treatable. Table 3 summarizes some managing strategies according to reviews (70,76,79–83) and our own clinical experience.

Medically serious side effects

Medically serious side effects (excluding toxicity) include chronic renal insufficiency and thyroid disease. Table 4 summarizes risk factors, medical markers and management strategies.

Thyroid and Parathyroid

Lithium's thyroid effects can occur early in treatment, but often appear after years of use as well. Women over 40 and rapid cyclers have higher risk of thyroid disfunction (70). Lithium has a direct reversible antithyroid effect, and thus it can lead to hypothyroidism (2-10% of patients) (84). It inhibits the thyroid gland's sensitivity thyroid stimulating hormone (TSH). High TSH levels on laboratory tests indicates a need to either discontinue lithium or supplement it with thyroid hormone replacement. Either T4 or T3 formulations can be use, alone or in combination; the most common practice is to use T4 (l-thyroxine), since it is metabolized in the body to T3 naturally.

Lithium increases the release of parathyroid hormone which rises blood calcium concentration (85) and increases calcium absorption (85). Hypercalcemia is infrequent but calcium levels should be monitored yearly, and tested if signs and symptoms of hypercalcemia (fatigue, weakness, abdominal

pain, bone pain, kidney or biliary calculus) occur (13,86).

Kidney

Lithium-related chronic renal insufficiency (CRI) occurs in 1-5% of persons after 10-20 years of treatment, interacting with effects of normal aging (7,87). End-stage renal failure occurs in 0.53% of lithium-treated individuals compared to 0.2% in the general population (12), and bias cannot be excluded (88). These numbers are important, since many clinicians and patients mistakenly believe that most people treated with lithium long-term develop kidney impairment. In fact, 95% or so have no clinical renal harm at all, even with long-term treatment. Nonetheless, even the harm in 1-5% can be and should be mitigated.

Chronic renal insufficiency is defined as glomerular filtration rate <60 mL/min at least twice in 3 months (77,87). This result tends to correlate with creatinine levels gradually approaching 2.0 mg/dL. In the setting of worsening azotemia exceeding 1.5 mg/dL on multiple occasions, or an increase in creatinine levels in ≥3 occasions (89), consideration of treatment alternatives should occur. Such outcomes are not an absolute contraindication to lithium use, though. Frequently, lithium can safely be continued at lower doses, as long as creatinine levels stabilize (76,89).

The key to prevention of lithium-related CRI is to modify modifiable risk factors, the most important of which are multiple daily dosing, overall dose, acute lithium toxicity, and duration of lithium treatment (90–93). Lithium should be dosed only once daily, as described above based on its long half-life, but also because such dosing allows for long periods over 24 hours where the kidney is exposed to very low doses of lithium. Repeated dosing of lithium multiple times daily maintains high blood levels, which is more harmful to the kidney (7,76,91,94). These kidney risks are a central reason why lithium should be dosed almost always once daily, not multiple times per day.

Of course, the lower the overall dose, the less the harm to the kidney. Thus the 1-5% long-term CRI risk cited here relates to standard doses of about 900 mg/d of lithium carbonate. If 600 mg/d were used, then the risk presumably would be lower. And at the very low doses suggested for dementia or suicide prevention, of about 25 mg/d equivalent of lithium carbonate, the long-term kidney risks of lithium may be very small indeed. The occurrence of acute lithium toxicity leads to

the immediate death of nephrons, reducing kidney reserve to withstand normal aging-related death of nephrons. Prior acute lithium toxicity is a known risk factor long-term CRI. Hence, keeping lithium levels below the toxicity range is another important factor in prevention of CRI.

Finally, a possible harm from once daily dosing may be that at standard doses, such as 900 mg/d lithium carbonate, an initial high peak of lithium level may occur. This effect may be mitigated by the use of a slow-release preparation, such as generic lithium carbonate ER, which smooths off the peak and keeps the kidney from exposure to brief but high lithium levels.

Laboratory tests

It is advisable to check thyroid, kidney function tests, serum electrolytes including calcium, and blood count, upon beginning lithium, and again about three months later, and then every 6 months in maintenance treatment (66,95). Given space limitations, further detail on monitoring is not provided here, and can be accessed by clinicians in other standard texts and other sources (e.g., Up-to-Date or other digital references).

Summary

Lithium may be the most effective psychotropic medication today, since it has disease-modifying benefits, not just symptom improvement. These clinical benefits occur in five main groups: bipolar illness, unipolar depression, suicide prevention, mood temperaments, and dementia prevention. Outside of bipolar illness, its other four benefits are not widely appreciated and deserve more attention. These benefits must be weighed against harms, of course, which are mainly nuisance and medical. Lower dosing of lithium mitigates many of these harms, while preserving many of its important benefits. More frequent use of lithium, at lower doses than has been common practice, may lead to much better clinical outcomes for a range of psychiatric conditions than is currently the case.

Table 1. Summary Clinical Guidance: Key Recommendations

1. For bipolar illness, lower levels often can be used in type II illness than type I.
2. For unipolar depression, lithium has preventive efficacy by itself, without standard antidepressants. In fact, it is better proven for prevention of unipolar depressive episodes than standard antidepressants.
3. For suicide prevention, lithium is the only treatment in psychiatry proven to prevent completed suicide, and it likely does so at any dose (including very low doses of 25 mg/d lithium carbonate equivalent).
4. For dementia prevention, lithium, unlike all other psychotropic medications, has been shown to reduce the multiple-fold elevated risk in patients with mood disorders back to population norms. It may have dementia prevention benefits at any dose (including very low doses of 25 mg/d lithium carbonate equivalent).
5. In rapid-cycling, lithium is not less effective than standard anticonvulsants.
6. In older persons, a therapeutic lithium level is about half what it would be in younger persons (ie. 0.4, not 0.8 mmol/L).
7. In mood temperaments, like cyclothymia or hyperthymia, lithium should be doses at about half the standard doses used in bipolar illness.
8. Lithium should not be dosed to a "therapeutic" level; it should be dosed to clinical efficacy.
9. There is no general minimum effective dose of lithium.
10. Chronic renal insufficiency happens in 5% or less of persons treated with lithium continuously for 20 years or longer.
11. The most effective way to prevent kidney impairment is to dose lithium once daily, not multiple times per day, and to give it at the lowest effective dose.

Table 2. Indications and target levels in lithium treatment

Indications for Lithium		Target level (Therapeutic Range)*	
		Acute	Maintenance (Prevention)
Bipolar illness			
	Mania	0.8 (0.6 – 1.0)	0.6 (0.4 – 1.0)
	Depression (type I)	0.8 (0.6 – 1.0)	0.6 (0.4 – 1.0)
	Depression (type II)	0.6 (0.4 – 1.0)	0.6 (0.4 – 1.0)
Unipolar depression		0.6 (0.4 – 1.0)	0.6 (0.4 – 1.0)
Cyclothymia/Hyperthymia		0.4 (0.2-0.6)	0.4 (0.2-0.6)
Suicide prevention			ND
Dementia			ND

**Lithium levels in mmol/L, ND = not detectable (levels below 0.2 usually are not detectable with standard laboratory testing)*

Table 3. Nuisance side effects and management strategies

Side Effect	Management strategy
Tremor	Lower dose, add propranolol, consider benzodiazepines. Minimize caffeine.
Sedation and cognitive impairment	Lower dose, consider multiple smaller doses, give highest dose at bedtime
Weight gain	Lower dose
Dry mouth	Consider glycerin-based oral moisturizers
Nausea/vomiting/diarrhea	Lower dose, take with food, use slowed release preparations or lithium citrate formulation.
Polydipsia/polyuria	Lower dose. Use once daily slow release formulations. Treat using thiazide diuretics, like amiloride 5mg bid or the hydrochlorothiazide /triamterene combination. Since thiazide diuretics increase lithium levels, lithium doses should be decreased by about 30-50% in coadministration and levels followed
Edema	Lower dose. May use spironolactone with caution.
Acne	Lower dose. If needed, consider standard treatments but not isotretinoin (due to depressive/suicidal effects)

Table 4. Serious medical side effects: Focus on kidney and thyroid

Organ				Management strategy
	Prevalence	**Key risk factors**	**Evidence**	
Kidney	Chronic renal insufficiency: 1-5% End stage renal disease: 0.5%	Multiple daily dosing Overall dose Duration of exposure Acute lithium toxicity	Creatinine elevation consistently into the 1.5-2.0 mg/dL range	Once daily dosing Dose to clinical effect, not level, and use lowest possible doses Minimize duration of treatment if relevant Use slow-release formulations Avoid dehydration Adequate salt intake or lower doses if salt restriction, as in low calories diets Avoid or monitor use of NSAID, ACEIs, thiazide diuretics, and other relevant drugs (i.e. haloperidol, ketamine, metronidazole). If diuretics are needed, use with caution
Thyroid	Abnormal laboratory values: 25% Clinical hypothyroidism 4%	Female gender Age over 40 Family history of thyroid disease Thyroid autoimmunity Rapid cycling course	Elevated TSH Decreased T3 and/or T4. Hypothyroid symptoms (constipation, fatigue, weight gain, hair loss, intolerance to cold, memory alteration)	Lower dose Replace with Levothyroxine or Liothyronine (preferred if cognitive disfunction and/or fatigue is present) if: TSH > 10 mU/L on two occasions with no clinical symptoms, or TSH 4-10 mU/L with active mood symptoms If replacement therapy given: treat to a target TSH of ≈1.0 mU/L

ACEIs: Angiotensin-converting enzyme inhibitors; NSAID: Non-steroidal anti-inflammatory drugs

REFERENCES

1. Post RM. The New News about Lithium: An Underutilized Treatment in the United States. Neuropsychopharmacology. 2018 Apr;43(5):1174–9.

2. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14;

3. McKnight RF, de La Motte de Broöns de Vauvert SJGN, Chesney E, Amit BH, Geddes J, Cipriani A. Lithium for acute mania. Cochrane Database Syst Rev. 2019 Jun 1;6:CD004048.

4. Rybakowski JK. Challenging the Negative Perception of Lithium and Optimizing Its Long-Term Administration. Front Mol Neurosci. 2018;11:349.

5. Nivoli AMA, Murru A, Vieta E. Lithium: still a cornerstone in the long-term treatment in bipolar disorder? Neuropsychobiology. 2010;62(1):27–35.

6. Shorter E. The history of lithium therapy. Bipolar Disord. 2009 Jun;11(Suppl 2):4–9.

7. Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, et al. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. 2019 Jul 22;7(1):16.

8. Grof P, Grof E. Varieties of lithium benefit. Prog Neuropsychopharmacol Biol Psychiatry. 1990;14(5):689–96.

9. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet Lond Engl. 2011 Oct 8;378(9799):1306–15.

10. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. Bipolar Disord. 2000 Sep;2(3 Pt 2):261–8.

11. Won E, Kim Y-K. An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms. Int J Mol Sci. 2017 Dec 11;18(12).

12. Malhi GS, Tanious M, Das P, Berk M. The science and practice of lithium therapy. Aust N Z J Psychiatry. 2012 Mar;46(3):192–211.

13. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170.

14. Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010 Jan 30;375(9712):385–95.

15. Severus WE, Kleindienst N, Seemüller F, Frangou S, Möller HJ, Greil W. What is the optimal serum lithium level in the long-term treatment of bipolar disorder--a review? Bipolar Disord. 2008 Mar;10(2):231–7.

16. Kleindienst N, Severus WE, Greil W. Are serum lithium levels related to the polarity of recurrence in bipolar disorders? Evidence from a multicenter trial. Int Clin Psychopharmacol. 2007 May;22(3):125–31.

17. Severus WE, Kleindienst N, Evoniuk G, Bowden C, Möller HJ, Bohus M, et al. Is the polarity of relapse/recurrence in bipolar-I disorder patients related to serum lithium levels? Results from an empirical study. J Affect Disord. 2009 Jun;115(3):466–70.

18. Malhi GS, Gershon S, Outhred T. Lithiumeter: Version 2.0. Bipolar Disord. 2016;18(8):631–41.

19. Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord. 2019;21(5):394–409.

20. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. Mol Psychiatry. 2019;24(2):198–217.

21. Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. J Affect Disord. 2017 01;217:266–80.

22. Bschor T. Lithium in the treatment of major depressive disorder. Drugs. 2014 Jun;74(8):855–62.

23. Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH, et al. Lithium treatment for unipolar major depressive disorder: Systematic review. J Psychopharmacol Oxf Engl. 2019 Feb;33(2):167–76.

24. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Feb 20;391(10128):1357–66.

25. Borges S, Chen Y-F, Laughren TP, Temple R, Patel HD, David PA, et al. Review of maintenance trials for major depressive disorder: A 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry. 2014;75(3):205–14.

26. Ghaemi SN, Selker HP. Maintenance efficacy designs in psychiatry: Randomized discontinuation trials - enriched but not better. J Clin Transl Sci. 2017 Jun;1(3):198–204.

27. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol. 1999 Oct;19(5):427–34.

28. Smith KA, Cipriani A. Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. Bipolar Disord. 2017;19(7):575–86.

29. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013 Jun 27;346:f3646.

30. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ. 2005 Feb 19;330(7488):385.

31. Braun C, Bschor T, Franklin J, Baethge C. Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder. Psychother Psychosom. 2016;85(3):171–9.

32. Tondo L, Baldessarini RJ. Antisuicidal Effects in Mood Disorders: Are They Unique to Lithium? Pharmacopsychiatry. 2018 Sep;51(5):177–88.

33. Song J, Sjölander A, Joas E, Bergen SE, Runeson B, Larsson H, et al. Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder. Am J Psychiatry. 2017 01;174(8):795–802.

34. Kessing LV, Søndergård L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. Arch Gen Psychiatry. 2005 Aug;62(8):860–6.

35. Mauer S, Vergne D, Ghaemi SN. Standard and trace-dose lithium: a systematic review of dementia prevention and other behavioral benefits. Aust N Z J Psychiatry. 2014 Sep;48(9):809–18.

36. Vita A, De Peri L, Sacchetti E. Lithium in drinking water and suicide prevention: a review of the evidence. Int Clin Psychopharmacol. 2015 Jan;30(1):1–5.

37. Helbich M, Leitner M, Kapusta ND. Geospatial examination of lithium in drinking water and suicide mortality. Int J Health Geogr. 2012 Jun 13;11:19.

38. Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N. Lithium levels in drinking water and risk of suicide. Br J Psychiatry J Ment Sci. 2009 May;194(5):464–5; discussion 446.

39. Terao T, Goto S, Inagaki M, Okamoto Y. Even very low but sustained lithium intake can prevent suicide in the general population? Med Hypotheses. 2009 Nov;73(5):811–2.

40. Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M, et al. Lithium in drinking water and suicide mortality. Br J Psychiatry J Ment Sci. 2011 May;198(5):346–50.

41. Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res. 1990 May;25(2):105–13.

42. Blüml V, Regier MD, Hlavin G, Rockett IRH, König F, Vyssoki B, et al. Lithium in the public water supply and suicide mortality in Texas. J Psychiatr Res. 2013 Mar;47(3):407–11.

43. Sarai SK, Mekala HM, Lippmann S. Lithium Suicide Prevention: A Brief Review and Reminder. Innov Clin Neurosci. 2018 Nov 1;15(11–12):30–2.

44. Zilkens RR, Bruce DG, Duke J, Spilsbury K, Semmens JB. Severe Psychiatric Disorders in Mid-Life and Risk of Dementia in Late-Life (Age 65-84 Years): A Population Based Case-Control Study. Curr Alzheimer Res. 2014 Jul;11(7):681–93.

45. Byers AL, Yaffe K. Depression and Risk of Developing Dementia. Nat Rev Neurol. 2011 May 3;7(6):323–31.

46. da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry. 2013 Mar;202(3):177–86.

47. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: Population-based cohort study. Br J Psychiatry. 2015 Jul;207(1):46–51.

48. Kessing LV, Gerds TA, Knudsen NN, Jørgensen LF, Kristiansen SM, Voutchkova D, et al. Association of Lithium in Drinking Water With the Incidence of Dementia. JAMA Psychiatry. 2017 01;74(10):1005–10.

49. Vohringer PA, Barroilhet SA, Amerio A, Reale ML, Alvear K, Vergne D, et al. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. Front Psychiatry. 2013;4:87.

50. Forlenza OV, De-Paula VJR, Diniz BSO. Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders. ACS Chem Neurosci. 2014 Apr 25;5(6):443–50.

51. Tondo L, Hennen J, Baldessarini RJ. Rapid-cycling bipolar disorder: effects of long-term treatments. Acta Psychiatr Scand. 2003 Jul;108(1):4–14.

52. Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Heilbronner U, et al. Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder. JAMA Psychiatry. 2018 Jan;75(1):65–74.

53. Tolliver BK, Anton RF. Assessment and treatment of mood disorders in the context of substance abuse. Dialogues Clin Neurosci. 2015 Jun;17(2):181–90.

54. Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN. Treatment of mixed bipolar states. Int J Neuropsychopharmacol. 2012 Aug 1;15(7):1015–26.

55. Sproule BA, Hardy BG, Shulman KI. Differential Pharmacokinetics of Lithium in Elderly Patients. Drugs Aging. 2000 Mar 1;16(3):165–77.

56. Perugi G, Hantouche E, Vannucchi G. Diagnosis and Treatment of Cyclothymia: The "Primacy" of Temperament. Curr Neuropharmacol. 2017 Apr;15(3):372–9.

57. Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry. 1991 Dec;48(12):1082–8.

58. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 1999;60 Suppl 2:77–84; discussion 111-116.

59. Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry. 1998 Aug;59(8):405–14.

60. Baldessarini RJ, Tondo L, Floris G, Rudas N. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. Am J Psychiatry. 1997 Apr;154(4):551–3.

61. Pope M, Scott J. Do clinicians understand why individuals stop taking lithium? J Affect Disord. 2003 May;74(3):287–91.

62. Dixon JF, Hokin LE. Lithium acutely inhibits and chronically up-regulates and stabilizes glutamate uptake by presynaptic nerve endings in mouse cerebral cortex. Proc Natl Acad Sci U S A. 1998 Jul 7;95(14):8363–8.

63. Malhi GS, Outhred T. Therapeutic Mechanisms of Lithium in Bipolar Disorder: Recent Advances and Current Understanding. CNS Drugs. 2016;30(10):931–49.

64. Hayward P. Lithium reverses tau pathology in Drosophila. Lancet Neurol. 2004 May 1;3(5):265.

65. Schou M. Serum lithium monitoring of prophylactic treatment. Critical review and updated recommendations. Clin Pharmacokinet. 1988 Nov;15(5):283–6.

66. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). American Psychiatric Pub; 2002.

67. Shulman KI, Almeida OP, Herrmann N, Schaffer A, Strejilevich SA, Paternoster C, et al. Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report. Bipolar Disord. 2019;21(2):117–23.

68. Ghaemi N. Clinical Psychopharmacology: Principles and Practice. Oxford University Press, USA; 2019.

69. Haussmann R, Bauer M, von Bonin S, Grof P, Lewitzka U. Treatment of lithium intoxication: facing the need for evidence. Int J Bipolar Disord [Internet]. 2015 Oct 22 [cited 2019 Dec 8];3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4615994/

70. Virani AS, Bezchlibnyk-Butler K, Jeffries J. Clinical Handbook of Psychotropic Drugs. 18th edition. Hogrefe & Huber Publishers; 2009.

71. Singh LK, Nizamie SH, Akhtar S, Praharaj SK. Improving tolerability of lithium with a once-daily dosing schedule. Am J Ther. 2011 Jul;18(4):288–91.

72. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. J Clin Psychiatry. 1998;59 Suppl 6:13–9; discussion 20.

73. Girardi P, Brugnoli R, Manfredi G, Sani G. Lithium in Bipolar Disorder: Optimizing Therapy Using Prolonged-Release Formulations. Drugs RD. 2016 Dec;16(4):293–302.

74. Szklarska D, Rzymski P. Is Lithium a Micronutrient? From Biological Activity and Epidemiological Observation to Food Fortification. Biol Trace Elem Res. 2019 May;189(1):18–27.

75. Öhlund L, Ott M, Oja S, Bergqvist M, Lundqvist R, Sandlund M, et al. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. BMC Psychiatry. 2018 Feb 7;18(1):37.

76. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord [Internet]. 2016 Dec 17 [cited 2019 Dec 9];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5164879/

77. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. Int J Bipolar Disord. 2015 Dec;3(1):28.

78. Ott M, Forssén B, Werneke U. Lithium treatment, nephrogenic diabetes insipidus and the risk of hypernatraemia: a retrospective cohort study. Ther Adv Psychopharmacol. 2019;9:2045125319836563.

79. Lapierre YD. Control of lithium tremor with propranolol. Can Med Assoc J. 1976 Apr 3;114(7):619–20, 624.

80. Szmulewicz A, Samamé C, Caravotta P, Martino DJ, Igoa A, Hidalgo-Mazzei D, et al. Behavioral and emotional adverse events of drugs frequently used in the treatment of bipolar disorders: clinical and theoretical implications. Int J Bipolar Disord. 2016 Dec;4(1):6.

81. Ness-Abramof R, Apovian CM. Drug-induced weight gain. Timely Top Med Cardiovasc Dis. 2005 Oct 28;9:E31.

82. Morriss R, Mohammed FA. Metabolism, lifestyle and bipolar affective disorder. J Psychopharmacol Oxf Engl. 2005 Nov;19(6 Suppl):94–101.

83. Adam P. Evaluation and management of diabetes insipidus. Am Fam Physician. 1997 May 1;55(6):2146–53.

84. Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. Clin Pract Epidemiol Ment Health CP EMH. 2006 Sep 12;2:23.

85. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet Lond Engl. 2012 Feb 25;379(9817):721–8.

86. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013 Feb;15(1):1–44.

87. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, et al. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. Int J Bipolar Disord. 2017 Dec;5(1):27.

88. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. JAMA Psychiatry. 2015 Dec;72(12):1182–91.

89. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. BMC Nephrol. 2018 03;19(1):305.

90. Aiff H, Attman P-O, Aurell M, Bendz H, Schön S, Svedlund J. End-stage renal disease associated with prophylactic lithium treatment. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2014 Apr;24(4):540–4.

91. Castro VM, Roberson AM, McCoy TH, Wiste A, Cagan A, Smoller JW, et al. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2016 Mar;41(4):1138–43.

92. Aiff H, Attman P-O, Aurell M, Bendz H, Ramsauer B, Schön S, et al. Effects of 10 to 30 years of lithium treatment on kidney function. J Psychopharmacol Oxf Engl. 2015 May;29(5):608–14.

93. 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 years or more on lithium. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1994;9(9):1250–4.

94. Carter L, Zolezzi M, Lewczyk A. An updated review of the optimal lithium dosage regimen for renal protection. Can J Psychiatry Rev Can Psychiatr. 2013 Oct;58(10):595–600.

95. National Collaborating Centre for Mental Health (UK). Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care [Internet]. London: The British Psychological Society and The Royal College of Psychiatrists; 2014 [cited 2019 Dec 1]. (National Institute for Health and Care Excellence: Clinical Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK498655/