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REVIEW

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Why lithium should be used in patients with bipolar disorder? A scoping review and an expert opinion paper

Gaia Sampogna [a], Delfina Janiri[b], Umberto Albert[c], Filippo Caraci[d], Giovanni Martinotti[e], Gianluca Serafini [f], Alfonso Tortorella[g], Alessandro Zuddas[h,†], Gabriele Sani [i] and Andrea Fiorillo [a]

[a]Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy; [b]Department of Psychiatry, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Department of Psychiatry and Neurology, Sapienza University of Rome, Rome, Italy; [c]Department of Medicine, Surgery and Health Sciences, University of Trieste, Italy. Azienda Sanitaria Integrata Giuliano-Isontina - ASUGI, UCO Clinica Psichiatrica, Trieste, Italy; [d]Department of Drug and Health Sciences, University of Catania, Catania, Italy; Unit of Neuropharmacology and Translational Neurosciences, Oasi Research Institute - IRCCS, Troina, Italy; [e]Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti, Italy; Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield AL10 9AB, UK; [f]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy; IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [g]Department of Psychiatry, University of Perugia, Perugia Italy; [h]Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cagliari, Italy; [i]Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

ABSTRACT

Introduction: Lithium treatment is considered the gold standard for the long-term management of bipolar disorder and recurrent unipolar depression. It is also extremely effective in other psychiatric conditions characterized by impulsivity and aggression, and for the prevention of suicidal behaviours.

Areas covered: This paper provides a scoping review and an expert commentary regarding the use of lithium in adult patients. Available information about efficacy, tolerability, dosing, and switching is analyzed, and the strategies that may be most useful in real-world clinical settings are highlighted.

Expert opinion: Lithium is effective on different domains of bipolar disorder, including the long-term prevention of recurrences of affective episodes, management of acute mania as well as in the prophylaxis of all affective episodes. Lithium has been defined a 'forgotten drug,' since its use in routine clinical practice has been declined over the last 20 or 30 years. Reasons for this trend include lack of adequate training on the management of lithium side effects. Considering its efficacy, use of lithium in ordinary clinical practice should be promoted. Several strategies, such as using slow-release formulations, can be easily implemented in order to minimize lithium side effects and improve its tolerability profile.

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Personalization; mood stabilizer; treatment; efficacy; tolerability

1. Introduction

Lithium is the gold standard for the treatment of subjects with bipolar disorder, and it is also useful in patients with refractory unipolar depression, as well as in a variety of disorders characterized by impulsivity and aggression [1]. Moreover, lithium prevents suicidal behavior in patients with bipolar or major depressive disorder [2–5] and has neuroprotective properties for neurogenerative disorders [6–8].

Lithium has been used as medication since the late 19th century. The serendipitous discovery of its efficacy is due to John Cade, an Australian psychiatrist, who used lithium to treat individuals with mania and found rapid and dramatic improvements [9]. The idea of using lithium was based on the hypothesis that major mental disorders should be due to the lack or imbalance in some unidentified chemical substances. Although Cade's findings were considered promising, the side effects of lithium increased patients' non-compliance and its toxicity was even responsible of some deaths. However, the issue of toxicity was greatly reduced when lithium blood levels were measured through suitable tests. Furthermore, lithium salt – being a chemical agent – cannot be patented and therefore its commercial production was overlooked. All these aspects contributed to the poor dissemination of the use of lithium salts in ordinary clinical practice. In the United States use of lithium salts was banned until 1970. Meanwhile, lithium had become registered elsewhere: in France as lithium gluconate in 1961, in the United Kingdom as lithium carbonate in 1966, in Germany as lithium acetate in 1967, and in Italy as lithium glutamate in 1970 [10].

The introduction of reliable quantitative methods for monitoring serum lithium concentration was associated with a significant increase in the prescription of lithium in clinical practice. In fact, the opportunity to monitor serum concentration was essential due to the narrow therapeutic index of lithium [11,12]. In the following decades, several clinical trials,

CONTACT Gaia Sampogna gaia.sampogna@gmail.com Department of Psychiatry, University of Campania 'L. Vanvitelli', Naples, Italy

†Deceased

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Article highlights

- Lithium is the gold standard for the treatment of subjects with bipolar disorder, and it is also useful in patients with refractory unipolar depression, as well as in a variety of disorders characterized by impulsivity and aggression.
- According to the ISBD/IGSLI Task Force, the standard lithium serum levels should be 0.60-0.80 mmol/L in adult patients with bipolar disorder. The lithium serum levels should be reduced to 0.40-0.60 mmol/L in case of good response but poor tolerance, or to increase it to 0.80-1.00 mmol/L in case of insufficient response and good tolerance.
- Doses above 1.5 mM might lead to toxic effects, while life-threatening effects are seen above 3.5 mM.
- In recent years, patients with bipolar disorder have been mainly treated with antipsychotics, with an increase from 12.4% of outpatient visits for bipolar disorder in the 1997-2000 period to 51.4% in the 2013-2016 period. At same time, the prescription of mood stabilizers and lithium decreased from 62.3% (in the period 1997-2000) to 26.4% in the 2013-2016 period. These trends confirm the to rediscover the efficacy and tollerability of lithium treatment.
- Lithium is one of the single most effective treatments available in psychiatry, with side effects that can be easily managed, also using extended-release formulations.

reviews, and meta-analyses [13–16] confirmed the efficacy and effectiveness of lithium in the management of patients with bipolar disorders. As stated by Dennis Charney at Yale University during a meeting at the Psychopharmacologic Drugs Advisory Committee of the FDA: 'The miracle of lithium was not its treatment of acute mania … Neuroleptics, and even high-dose benzodiazepines, are quite effective for the treatment of this condition. The main issue of lithium is prevention of relapse.' Although lithium is among the single most effective treatments available in psychiatry, its side effects are easily manageable, and many patients stay on low dosages of lithium for decades, its true effectiveness has been overlooked, so that lithium has been defined for decades a 'forgotten drug' [17]. Furthermore, when other mood stabilizers such as atypical antipsychotics gained approval to market, a great shift towards these medications was observed, and lithium was less frequently used [18–20]. However, lithium remained an effective treatment strategy also in other serious clinical conditions characterized by internalizing and externalizing behaviours, due to its anti-impulsivity and antisuicidality effects. For example, lithium is used in clozapine-induced neutropenia, since it can increase colony-stimulating factors and the proliferation of pluripotent stem cells, and in the Klein-Levine syndrome, which is characterized by extreme somnolence alternate with megaphagia, psychiatric and behavioural symptoms. Lithium treatment is also used for psychogenic polydipsia and as augmentation strategy in treatment resistant patients with schizophrenia [21].

Lithium is used in different groups of patients with bipolar disorders, including adolescents, elderly people, patients with substance use disorders, and pregnant women. However, the use of lithium in these different populations should be adapted according to different socio-demographic and clinical characteristics, since the profile of efficacy, tolerability, and side-effects may be very different from one group to another. In fact, elderly people usually require lowdoses of lithium to achieve effective serum concentrations, due to pharmacokinetic modifications and to the reduced renal excretion. On the other hand, an increase of renal lithium excretion has been observed in pregnant women, which may require increased lithium doses to obtain the same effect; of course, the risk of toxicity of high doses of lithium should be balanced with the positive effects of increasing lithium dosage. These examples highlight the need for careful physical and laboratoristic examination of patients taking lithium, which cannot be restricted to the assessement of lithium serum levels.

Several studies have compared the efficacy/effectiveness and safety profile of antipsychotics with lithium (Sepede et al.,[22]; DelBello et al., [23]; Kadakia et al., [24]; Ogasawara et al.,[25]), confirming the potential role of atypical antipsychotics in patients with bipolar disorder. However, Hayes et al. [26] found a superiority of lithium treatment over atypical antipsychotic medications used in the maintenance phase of the disorder. The network meta-analysis by Kishi et al. [27] found that the combination of aripiprazole and valproate was the best treatment for reducing the recurrence/relapse rates of any mood episode and of depressive episodes in patients with bipolar disorder, with the association lithium/oxcarbazepine ranking high with respect to reduced recurrences/relapses.

Possible factors hampering the use of lithium in clinical practice include: its narrow therapeutic index; the profile of possible serious adverse events; patients' low adherence to blood monitoring; and the high rate of comorbid physical disorders in patients with bipolar disorder, with an increased risk for side effects. These factors could explain why many psychiatrists tend to prefer other mood stabilizers or atypical antipsychotics for the treatment of patients with acute affective episodes . Young residents in psychiatry are often untutored on lithium use and feel uncomfortable in prescribing it [28,29], although a greater awareness of lithium use has been recently reported [30–33].

Improving the quality and quantity of training, and increasing education and supervision on lithium subtleties for early career psychiatrists are possible strategies to 'rediscover' lithium and increases its use in clinical practice. In this expert opinion paper we aim to : 1) provide some essential information regarding the pharmacological profile of lithium and its neuroprotective effects; 2) summarize the overall efficacy of lithium treatment (with a special focus on adolescents, elderly patients, patients with substance use disorders and pregnant women); 3) discuss clinically relevant issues regarding dosage, management of side effects and potential differences according to lithium formulations; 4) provide some suggestions on how to improve the use of lithium in clinical practice.

2. Pharmacological profile of lithium

Lithium is generally administered as oral tablets at 0.4 to 2.0 g/day. It is well absorbed at the gastrointestinal level (i.e., stomach), with an oral bioavailability of 80–100% and it is excreted in urine. In order to have a therapeutic effect, lithium overcomes the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) [34].

Nowadays, the prolonged-release (PR) and immediate-release (IR) lithium formulations are available. The immediate-release formulations are rapidly absorbed and achieve

peak serum concentrations (Cmax) in 1–2 h after oral administration (tmax), while the tmax values for prolonged release are 4–5 h. Comparing the two formulations, the area under the serum concentration–time curve (AUC) values are similar. The most significant difference is the more stable lithium serum concentrations of prolonged released formulations [35].

Lithium has a narrow therapeutic window and a high incidence of troublesome side effects when plasma concentrations exceed the superior threshold. Lithium's most common side effects (plasma levels within the therapeutic range) include tremor, polyuria, polydipsia, hypothyroidism, hyperparathyroidism, weight gain, and diarrhea. Although these events occur in a minority of individuals taking lithium, they may induce some patients to poor treatment compliance or to interrupt the therapy [36–39]. Among those side effects, only tremors are due to the peak serum levels, with a peak at ½ h after the dose. Therefore, using prolonged release formulations can reduce fluctuations of serum plasma levels and its related side effects [40]. A recent randomized, multicenter, open trial, demonstrated that switching from immediate-release to prolonged-release lithium significantly reduces tremor after one week treatment in patients with bipolar disorder [41,42].

Lithium does not bind serum protein and has a distribution volume of about 0.7–1.0 L/kg. It is not metabolized by liver cytochromes and is eliminated as free ion at renal level. Several interactions – both pharmacokinetic and pharmacodynamic [43] – have been described. The most clinically relevant pharmacokinetic drug interactions occur when lithium is co-administered with drugs reducing renal elimination, such as thiazide and loop diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs] and angiotensin-converting enzyme [ACE] inhibitors [44]. Pharmacodynamic drug interactions are less frequent and may occur when combining lithium with: i) selective serotonin reuptake inhibitors (SSRI) (i.e., increased risk of serotonergic syndrome); ii) first-generation antipsychotics (i.e., haloperidol) with increased laboratory markers of oxidative stress and neurotoxicity [43]. In particular, some drugs, such as SSRI, NSAIDs, ACE inhibitors, angiotensin-II receptor antagonists, thiazides, spironolactone, furosemide, metronidazole, tetracyclines, topiramate, may increase serum levels of lithium concentrations. On the contrary, theophylline, caffeine, sodium bicarbonate, and products containing sodium chloride may decrease lithium concentrations. Antipsychotics may worsen lithium neurotoxicity, while calcium channel blockers may cause ataxia, confusion, and somnolence.

According to the recent recommendations issued by the ISBD/IGSLI Task Force on treatment with lithium in adult patients with bipolar disorder, the standard lithium serum level should be 0.60-0.80 mmol/L, with the option to reduce it to 0.40-0.60 mmol/L in case of good response but poor tolerance, or to increase to 0.80-1.00 mmol/L in case of insufficient response and good tolerance [45–47]. Doses above 1.5 mM might lead to toxic effects, while life-threatening effects are seen above 3.5 mM [48].

Despite its widespread use, the mechanism of action of lithium at both clinical and molecular levels still needs to be fully elucidated [49]. Lithium can reduce excitatory dopaminergic and glutamatergic neurotransmission and increase GABAergic transmission. At intracellular level, lithium targets several second-messenger systems, including the adenyl cyclase, phospho-inositide pathways, and protein kinase C, reducing excessive excitatory neurotransmission. Lithium increases the production of brain-derived neurotrophic factor (BDNF), which is essential for neuronal development and also induces the release of Transforming-Growth-Factor-β1 (TGF-β1) from astrocytes and its activation [50–55].

In the last twenty years, numerous studies have examined the putative neurotrophic and neuroprotective effects of lithium [6,56–67]. Although the molecular mechanisms underlying the neuroprotective efficacy of lithium are still unclear, it has been hypothesized that lithium inhibits apoptotic pathways via GSK-3β, protects against glutamate excitotoxicity and, most importantly, may positively modulate neurotrophic signaling pathways, such as BDNF and TGF-β1 pathways.

3. Overall efficacy of lithium treatment

This is a scoping review aiming to summarize the clinical overall efficacy of lithium treatment and specifically in different groups of patients with bipolar disorder. The following keywords 'bipolar disorder,' 'lithium treatment,' 'adolescent,' 'elderly,' 'pregnancy,' 'substance use,' 'efficacy,' 'safety,' 'tolerability,' 'side effects' were entered in PubMed, ISI Web of Knowledge, Scopus, and Medline. Terms and databases were combined using the Boolean search technique, which consists of a logical information retrieval system (two or more terms combined to make searches more restrictive or detailed). Based on this strategy, we found that lithium showed its efficacy on different domains of bipolar disorder, in particular on the long-term prevention of recurrences of affective episodes [68–70], management of acute maniac and (to a less degree) acute depressive episodes; in addition, lithium has strong effects in the prophylaxis of all affective episodes [71].

A satisfactory mood stabilization over 6–12 months may be reached by two thirds of patients with bipolar disorder receiving lithium, and an *excellent response* (no episodes on lithium monotherapy over a ten-year period) has been found in approximately one-third of patients [72].

The use of lithum as preventive strategy for manic and depressive recurrences has been tested in several placebo-controlled, randomized, long-term trials lasting at least 18 months [73,74]. All these studies found that the long-term risk of a new manic or depressive episode was significantly lower with lithium compared to placebo, with a higher effect for manic than for depressive episodes (that means that lithium is indeed significantly more effective than placebo in preventing depressive episodes, but it is more effective in preventing mania than depression, with a manic/depressive episode protection ratio of 2.49) [68].

The efficacy of lithium in treating acute bipolar depression has been recently questioned: a meta-analysis [75] on the use of lithium in acute bipolar depression, including more than 1,500 patients, found no statistically significant difference between lithium vs. antidepressants or placebo. On the other hand, a sensitivity analysis performed by the same authors (double-blinded, monotherapy, cross-over studies) demonstrated the specificity of lithium for bipolar depression than for unipolar depression. The treatment of bipolar depression is

a challenge for clinicians, as all compounds are poorly effective or take longer to be effective; this is why recent guidelines (e.g., the Australian and New Zealand College of Psychiatrists clinical practice guidelines) [76] still consider lithium as a first-choice mood stabilizer even for acute bipolar depression.

In a six-week, open-label, single-center trial, lithium was effective in treating comorbid anxiety in bipolar disorder, both as adjunct and in monotherapy [77].

The long-term effectiveness of lithium, compared to mood stabilizers and/or atypical antipsychotics, has been demonstrated both in *relapse-prevention studies* as well as in *prophylaxis studies*. In particular, in the former study design, only individuals who acutely responded to the studied drugs are eligible to enter the randomization maintenance phase (enriched design), while in *prophylaxis studies*, any euthymic patient can be eligible – regardless of the previous pharmacological treatment – and can be randomized to the drug or to placebo during the prophylaxis period. These studies confirm that lithium is indeed effective for the prophylaxis of new episodes in all patients with bipolar disorder (BD), irrespective to what compound has been used to treat the acute episode and even in patients who are euthymic without any drug when you start prophylaxis maintenance treatment) [78,79].

Hsu et al. [80] recently confirmed that lithium has significant preventive effects on the recurrence of major affective episodes in patients with serum levels of 0.4–0.8 mmol/L. The dose-response analysis showed that the risk of affective episodes decreases with the increase of lithium serum levels (linear model Odds Ratio - OR: 0.85, for every 0.1 mmol/L increase; non-linear model OR: 1.00 at 0.0 mmol/L, 0.42 at 0.4 mmol/L, and 0.27 at 0.8 mmol/L). Beyond the established efficacy of lithium in long-term term stabilization of BD, several studies and meta-analyses confirmed that lithium prevents suicide and suicide attempts in patients with bipolar disorder or depression, and that this effect is partly independent of lithium's effects on mood [81–85]. Moreover, a recent meta-analysis has confirmed the protective association between high levels of lithium concentration in drinking water and global mortality rates due to suicide. This finding further supports the anti-suicidal properties of lithium [86].

As a consequence, several clinical guidelines or practice recommendation papers consider lithium the first treatment choice when suicidal risk is high. According to the VA/US Department of Defense Clinical Practice Guideline for Assessment and Management of Patients at Risk for Suicide 'lithium alone (among patients with bipolar disorder) or in combination with another psychotropic agent (among patients with unipolar depression or bipolar disorder) may be offered to patients in order to decrease the risk of death by suicide .' Lithium may be maintained together with another mood stabilizer even when as monotherapy it failed to prevent mood episodes if the risk of suicide is high: in that case, it will reduce the risk of suicide while another compound will contribute to the long-term stabilization of the patient [70].

The BALANCE multicentric trial [87], involving more than 300 patients with bipolar I disorder (aged 16 or older), included an open-label lithium or valproate monotherapy, or a combination of both. The need for starting a new intervention due to the presence of a new affective episode was selected as primary outcome of the study. In this open-label trial, lithium monotherapy and its combination with valproate are more likely to prevent relapse than valproate monotherapy.

Recently, the Pharmacogenomics of Bipolar Disorder (PGBD) study including eleven participating sites, aimed to identify clinical predictors of lithium response [88]. In this study, patients stabilized with a lithium-based monotherapy have been invited to participate. Several clinical predictors of lithium treatment failure have been identified, including baseline anxiety symptoms, functional impairment, negative life events and lifetime clinical features, such as history of migraine, suicidal ideation/attempts, and mixed episodes. Future validation is needed to confirm these clinical predictors of treatment failure and their clinical use.

A multi-site trial by Budick et al. [89] in a large group of adult patients with bipolar disorder has further confirmed the efficacy of lithium treatment and its effect on global neurocognitive functioning. In particular, the authors found that lithium treatment does not impair neurocognitive functions in patients with BD; on the contrary, patients reported a significant improvement in the performances across all cognitive tests. At baseline, no differences were found between patients treated with lithium and those treated with other medications, confirming that lithium does not impair cognition in patients with bipolar disorder and can improve neurocognitive functioning.

In the Bipolar CHOICE trial [90], a mixed sample of outpatients with bipolar I or II disorder were randomized to receive lithium or quetiapine. The different therapeutic approaches were evaluated in terms of changes at the Clinical Global Impressions-Efficacy Index. In this study, very limited exclusion criteria have been used in order to maximize generalizability; a flexible dosing regimen of antipsychotic medications was adopted in order to be as close as possible to the real world practice. The authors concluded that there were no differences between lithium and quetiapine, although the former was better tolerated in terms of frequency, intensity, and side effects. Moreover, in the LiTMUS trial, Nierenberg et al. [91] found that the augmention with low-dose lithium to other mood-stabilizing treatment did not result in additional treatment effects.

In a study carried out with 42 real-world bipolar patients, Gao et al. [92] found a minimal difference in effectiveness between lithium and quetiapine IR monotherapy.

In the SMART trial, Gao et al. [93] highlighted that an adjunctive therapy with lamotrigine and quetiapine should be initiated as early as possible in patients treated with lithium when depression symptoms are present. In the study by Bowden et al. [94], lithium treatment did not significantly separate from placebo for risk to recurrence in time to any affective episode, neither for risk to recurrence in time to maniac or depressive episode.

The efficacy of lithium treatment has been evaluated also in rapid cycling patients. Calabrese et al. [95] found that there are no large differences in efficacy between lithium and divalproate in the long-term treatment of rapid cycling bipolar

disorder. In addition, lamotrigine has the potential to complement the spectrum of lithium and divalproate through its greater efficacy for depressive symptoms.

In the treatment of acute mania, lithium has been used in loading strategies, with a rapid and effective effect. In fact, loading strategy has potential benefits, including rapid symptom reduction in mania and shortened length of stay. Disadvantages include an increased likelihood of adverse effects of the medications [96].

Several observational trials have confirmed lithium's anti-suicidal effects, with fewer suicides or attempts in patients treated with lithium than without. Such data has been confirmed in randomized clinical trials including the presence of suicidal behaviors as adverse outcomes [97,98]. Several mechanisms of action have been proposed for explaining the anti-suicidal effects of lithium. In particular, the agonistic properties of lithium on serotonin receptors can counterbalance the dysfunction in corticotrophin-releasing hormone and in noradrenergic and serotonergic systems, which are implicated in suicidal thinking. Other possible mechainsms of actions include the increase in the release of glutamate and the activation of GABAergic systems. Moreover, a role in the reduction of suicidal risk can be attributed to the increased contact with healthcare providers due to constant blood monitoring of lithium concentrations.

3.1. Efficacy of lithium: data from real-world studies

In recent years, a vast amount of data have been collected on the efficacy of lithium treatment in real-world studies, which are studies with few or no exclusion criteria, evidence-based selection of medications, lack of placebo group. A recent study by Köhler-Forsberg et al. [99] in a sample of outpatients with bipolar disorder found that the clinical improvements were similar in patients receiving lithium alone compared to patients receiving an association of lithium+antipsychotics. The secondary analyses showed that patients treated with lithium+antipsychotics may have better improvement than those treated with lithium+anticonvulsants. However, those treated with the combination treatment showed a worse glycid profile as well as a higher risk of developing the metabolic syndrome compared to those receiving lithium monotherapy.

Although lithium is effective in patients with bipolar disorder, a relevant obstacle to full recovery is the lack of adherence to treatment patterns. In fact, Inoue et al. [100] in a sample of 13,788 patients with bipolar disorder treated with lithium, sodium valproate, lamotrigine or aripiprazole, found that the rate of discontinuation for prescribed mood stabilizers and atypical antipsychotics was similarly low.

Finally, in a real-world study focused on all-cause hospitalization risk in patients with bipolar disorder, Lähteenvuo et al. [101] found the lowest risk in those treated with lithium (Hazard Ratio - HR, 0.71 [95% CI, 0.66–0.76]). The most frequently used antipsychotic treatment, quetiapine fumarate, showed only modest effectiveness (risk of psychiatric rehospitalization: HR, 0.92 [95% CI, 0.85–0.98]; risk of all-cause hospitalization: HR, 0.93 [95% CI, 0.88–0.98]). Results from sensitivity analyses showed consistent beneficial effects only for lithium.

3.2. Efficacy of lithium in adolescent and pediatric patients

Seminal studies on the efficacy of lithium in adolescent patients have been carried out by Kowatch et al. [102] and by Geller et al. [103]. In particular, Kowatch et al. [102] found that adolescents aged 8–18 years reported a response rate of 38% when treated with lithium. In the study by Geller et al. [103], including 6- to 15-year-old children and adolescents with a DSM-IV bipolar I disorder in manic or mixed phase, response rate was higher in those treated with risperidone compared to lithium (68.5% vs 35.6%). However, higher levels of side effects – including weight gain and increased prolactin levels – occurred in those treated with risperidone.

Only in 2018 the US FDA approved lithium for the treatment of mania in young subjects with bipolar disorder aged 12–17 years. The Collaborative Lithium Trials (CoLT1 and CoLT2) explored the most effective dosing strategies for young individuals with bipolar disorder, and found that serum levels of lithium up to to 1.0 mEq/L are well tolerated.

Lithium has been the first agent which was investigated as maintenance treatment in adolescents with bipolar disorder. In a 18-months naturalistic study [104], adolescents receiving lithium had a lower risk of relapse compared to those discontinuing lithium treatment. Findling et al. [105] reported that lithium was superior to quetiapine in preventing affective episodes and was also associated with higher levels of personal and social functioning. Similar findings regarding efficacy of lithium treatment in both adolescent and adult patients with bipolar disorder suggest that those data can be used also for inform the use of lithium in pediatric population [106].

In a six-week study by Patino et al. [107], adolescent bipolar patients with acute maniac/mixed episode were treated with lithium or with quetiapine. At final endpoint, both pharmacological treatments led to clinical improvement. The head-to-head comparison showed that quetiapine was associated with a statistically significant greater rate of response and overall symptom reduction compared with lithium. However, in less than half of the participants symptomatic remission was achieved, regardless the type of treatment received.

Lithium has been approved by FDA to be used in pediatric bipolar disorder from the age of seven years old. Several pediatric trials have confirmed the efficacy of lithium in acute mania, depressive symptoms and in the management of disruptive behavior in children with conduct disorder. Optimal dosing strategies have been extensively studied. For children aged from 7 to 17 years old, the treatment should be started with lithium 300 mg two or three/times per day, and the dosage can be increased by 300 mg weekly thereafter, as tolerated. The target serum concentrations should range from 0.8 to 1.2 mEq/L, with toxic effects and cessation of dose escalations occurring between 1.2 and 1.4 mEq/L [108,109].

3.3. Efficacy of lithium in elderly patients

A few studies are available on elderly patients with bipolar disorder, although almost 25% of adults bipolar patients are over 65 [110].

Clinicians treating the increasing numbers of bipolar elders with mood stabilizers need evidence from age-specific randomized controlled trials. A seminal work including elderly patients suffering from bipolar disorder has been carried out by Young et al. [111], who assessed tolerability and efficacy of lithium carbonate and compared it with divalproex. Attrition rates were similar in patients receiving lithium and in those receiving divalproex. Patients receiving lithium reported a higher symptomatological improvement compared with those treated with divalproex.

In a review evaluating data from national and international guidelines, Dols et al. [112] highlighted that the majority of the guidelines do not include specific sections dedicated to the treatment of elderly patients with bipolar disorder. However, lithium is widely used in elderly subjects with bipolar disorder, both in patients with euphoric mania and individuals with minimal comorbid neurological disorders. Due to its neurotrophic effects, lithium is associated with a reduced risk of cognitive decline and of developing dementia [113]. Moreover, a recent meta-analysis has highlighted the potential role of lithium treatment in lowering the risk of stroke among adults with bipolar disorder, due to its antioxidant activity and endothelial action, which should further encourage the use of this medication in elderly population [114].

Among potential pleiotropic effects of lithium treatment in elderly patients, some recent studies [115,116] highlighted that lithium reduces the risk of osteoporosis in treated elderly patients.

Lithium is considered an effective therapy for manic and depressive episodes and relapse prevention of affective episodes in elderly patients with bipolar disorders. Among the few trials carried out with elderly patients, a controlled trial evaluating the efficacy of lithium vs. valproic acid in acute mania and a post-hoc analysis of maintenance trials have been found. Lithium is superior to valproic acid in reducing the severity of maniac symptoms, and it is associated with a significantly delayed time to intervention for mania/hypomania/mixed episodes in comparison to placebo, but not for time to intervention for depression.

A recent trial including elderly veterans affected from bipolar disorder found no difference in terms of days until discontinuation in those treated with lithium compared to those treated with second-generation antipsychotics [117].

When treating elderly patients with lithium, it is necessary to consider that pharmacodynamic and pharmacokinetic factors change with age and there is a higher risk of side effects and drug interactions. Moreover, the distribution volume is higher in old age, with a reduced renal clearance and a twofold prolonged elimination process requiring a lower dose of one-third to one-half. Therefore, when initiating lithium a slow increase in dosage is recommended. Interactions with other medications, such as thiazide diuretics, ACE inhibitors and NSAID that are known to increase lithium plasma concentration should be carefully considered [43].

In elderly patients with bipolar disorder, lithium remains the first-line therapy for the maintenance treatment in monotherapy; the daily dose of lithium should be 25–50% of the daily dose recommended for adults. In elderly patients, it is recommended to keep serum levels of lithium between 0.4 and 0.6 mmol/l [47,118].

3.4. Efficacy of lithium in patients with substance use disorders

The association between BD and substance use disorder (SUD) has been extensively studied [119]. One of the largest studies, conducted as part of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), evidenced high prevalences of alcohol abuse in subjects with DB-I (58%), and any other substance (38%) [120]. However, only few studies have been conducted evaluating possible pharmacological strategies in these patients. Geller et al. [121] conducted two placebo-controlled trials and found that the adjunct of valproate to lithium in bipolar patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms; moreover, lithium treatment improves mood and SUD symptoms in bipolar adolescents.

Given the high rate of bipolar disorder and SUD comorbidity, more research on the treatment of this population is needed. Moreover, BD and SUD share altered levels of impulsivity [122] that compromises the psychophysical state of the individual and the propensity for risky behaviors. Specifically, double-blind placebo-controlled trials are needed to establish the effectiveness of medications found to be effective in open-label trials.

A recent study by Gadh [123] found that the introduction of low-dose lithium in patients treated in an addiction treatment setting (where people were not necessarily affected from bipolar disorder) was useful in helping them to achieve and maintain progress in their lives.

New studies are needed to identify those medications which may treat either both bipolar disorder and SUD. Moreover, it may be advisable to include patients with prior SUD in clinical trials for evaluating the effectiveness and safety of new medications in patients with bipolar disorder and SUD.

3.5. Use of lithium in pregnant women

In pregnant women, it is necessary to monitor lithium serum levels on a monthly basis, while in the last trimester, the monitoring should be weekly [124,125]. Moreover, recent observational real-world studies have found that it is not necessary to decrease or stop lithium treatment before delivery, but it should be sufficient to assess serum levels twice weekly, at least for the first two weeks after delivery [125,126].

Clinicians should discuss with pregnant women affected from bipolar disorder the risks and benefits of continuing lithium treatment in anticipation of pregnancy and after childbirth, as well as during breastfeeding [127].

In cases of lithium discontinuation during pregnancy, lithium treatment should be rapidly reintroduced following childbirth, since early post-partum period is associated with a high risk of affective recurrences [128,129]. After childbirth, lithium serum levels should be increased at 0.8–1.0 mEq/L, in

order to reduce the risk of relapses and should be checked on a weekly basis for at least one month.

The use of lithium during early pregnancy has been previously associated with an increased risk of Ebstein's anomaly, but a recent cohort study involving 1,325,563 pregnancies in women have specifically examined this risk. Patorno et al. [130] have studied the risk of cardiac malformations among infants exposed to lithium during the first trimester as compared with unexposed infants and also the risk in infants exposed to lamotrigine. The authors concluded that the magnitude of the cardiac malformations is smaller as compared to that observed in the past. The incidence of cardiac malformations is 2.4% in infants exposed to lithium vs. 1.4% in infants exposed to lamotrigine (1.4%) vs. 1.2% in those non exposed.

4. Clinically relevant issues (i.e. dosage and side effects) and differences according to the formulation

According to several international guidelines [131–133], the gold standard treatment for patients suffering from bipolar disorders is represented by lithium, although it has a narrow therapeutic range [11,134]. Therefore, the approach to each patient with bipolar disorder should be individualized in order to identify the dose useful to achieve the maximum symptom reduction with tolerable side effects. It is necessary to regularly monitor the serum levels of lithium as well as thyroid and renal functioning [135–140].

In elderly subjects with bipolar disorder, lithium is associated with a higher number of adverse effects compared to younger individuals. Common adverse events are weight gain, cognitive dysfunction, sedation, renal and thyroid alterations, and tremors. Patients treated also with other drugs such as thiazide or loop diuretic and ACE inhibitors should be carefully monitored for side effects. People suffering from multiple physical comorbidities are at higher risk of developing lithium toxicity.

The most common side effects of lithium include lithium-induced nephrogenic diabetes insipidus and lithium nephropathy (defined also as renal insufficiency). If untreated, these conditions can be potentially lethal. A study by Bocchetta et al [141] highlighted that duration of lithium treatment should be considered as an additional risk factor for renal adverse effect, in particular in elderly patients with a reduced glomerular filtration rate. However, renal dysfunction tends to appear after decades of treatment and to progress slowly and irrespective of lithium continuation.

In order to prevent renal side effects, the once-daily dosing schedule should be preferred, selecting the lowest serum lithium level associated with clinical effectiveness, so to prevent lithium intoxication (Schoot et al., [142]). However, a close and continuing collaboration among psychiatrists, nephrologists, patients, and their carers is essential in order to promptly identify any side effect [143].

4.1. Standard lithium workup and monitoring

Lithium treatment can be easily implemented in ordinary clinical practice, both at inpatient and outpatient level. The following aspects should be kept into consideration:

1. Before starting treatment with lithium, it is recommended to measure blood concentrations of creatinine and urea-nitrogen in order to check renal functioning, the levels of electrolytes (sodium, potassium, calcium), and the levels of thyroid and parathyroid hormones, as well as obtaing an electrocardiogram.

2. The therapy should be started by using one daily dose and slow-release formulation should be preferred.

3. The optimum dosage of lithium should be based on the evaluation of each individual patient, combining clinical response with the serum levels of lithium.

4. Lithium blood concentration should be checked five days after the targeted dose is achieved. The lithium blood concentration level can be repeated until lithium reaches its therapeutic levels. Afterwards, lithium, creatinine, and TSH levels should be checked every one to two months in the first six months, and then every 6–12 months, or as clinically indicated.

5. Sampling of lithium concentration should be done exactly 12 hours after the most recent lithium dose. As suggested by the ISBD IGSLI Task Force Treatment [144], when using the twice/daily dosing, the serum level should be assessed in the morning 12 ± 1 hours after intake of the (last) evening dose and before the morning dose. If patients are treated with once daily evening dose, the assessment of lithium serum levels should be done in the following morning, 12 + 1 hours after the (single) evening dose.

Several short-term side effects can arise during the treatment. The most frequent include nausea, vomiting, and abdominal cramping, especially at the beginning of the treatment. Administering lithium treatment following the meal represents an useful strategy to easily manage these side effects, which are also self-limiting. Furthermore, neurological side effects – such as fine hand-tremors - can appear. The use of slow-release lithium formulation is effective in reducing the blood peak of lithium and therefore in decreasing the incidence of this side effect. Another common side effect is related to dysfunction at the thyroid level. Therefore, it is necessary to regularly monitor endocrine functioning, in order to promptly manage with hormonal substitute therapy this alteration. Finally, renal side effects can appear, including polyuria and polydipsia, which can be reduced by using slow-release formulation. However, it is essential to regularly check renal functioning, in order to monitor the long-term effect at renal level. In particular, as pointed out by McKnight et al. [145], lithium treatment is associated with increased risk of reduced urinary concentrating ability and glomerular filtration rate can be reduced up to −6, 22 mL/min (95% CI −14 ,65 to 2 ,20, p = 0 ,148). Moreover, lithium treatment can increase risk of renal failure with a small absolute risk.

Other side-effects associated with lithium treatment include clinical hypothyroidism (with odds ratio [OR] 5 ,78, 95% CI 2 ,00–16 ,67; p = 0,001), hyperparathyroidism with increased levels of blood calcium and parathyroid hormone, as well as weight gain. However, a population-based cohort study focused on the maintenance phase of bipolar disorder found that lithium treatment was associated with more renal and endocrine adverse side effects compared to other mood stabilizers, but the incidence of weight gain was lower [26]. Hayes et al. [146] found some

predictive factors of renal failure, including younger age at starting lithium therapy, female gender and lower baseline estimated glomerular filtration rate. Furthemore, it should be considered that the the risks of side effects should be balanced with the extremely high clinical efficacy of lithium and its anti-suicidal effects, which make it the first therapeutic option in patients with bipolar disorder [147,148].

6. Conclusions

Lithium still represents a relevant pharmacological agent in the treatment of patients with bipolar disorder, although for several decades its use has significantly decreased in clinical practice [149]. Lithium has been defined as the 'forgotten drug,' since it was not routinely prescribed by clinicians in ordinary clinical practice, due to the lack of adequate training in the management of its possible side effects. It is time to promote the appropriate use of lithium in ordinary clinical practice, considering that it represents one of the most effective treatment available in psychiatry, with several possible strategies to be implemented in order to minimize side effects and low tolerability profile.

7. Expert opinion

In recent years, the treatment of patients with bipolar disorder has been mainly based on the prescription of antipsychotics, increasing from 12.4% of outpatient visits for bipolar disorder in the 1997–2000 period to 51.4% in the 2013–2016 period. At the same time, the prescription of mood stabilizers and lithium decreased from 62.3% (in the period 1997–2000) to 26.4% in the 2013–2016 period [135]. These trends further confirm the need to rediscover the efficacy and tolerability profile of lithium .

In fact, lithium represents one of the single most effective treatments available in psychiatry, with side effects that can be easily managed, also using extended-release formulations.

Furthermore, recent meta-analyses have also confirmed the potential neurotrophic and neuroprotective role of lithium, in terms of increase of the global grey matter volume in lithium-treated bipolar patients compared to lithium-free bipolar patients [65].

Lithium has proven to be effective in treating patients with bipolar disorder, in particular by reducing relapse risk of affective episodes.

Lithium demonstrated to be effective on different domains of bipolar disorder, in particular in the long-term prevention of recurrences of affective episodes [68–70], management of acute maniac and (to a less degree) acute depressive episodes; in addition, lithium has strong effects in the prophylaxis of all affective episodes [46,71].

The availability of new extended-release formulation provides potential advantages such as the progressive increase of lithium concentrations and the stability of serum concentrations. Both aspects are associated with a reduced risk of adverse events, while improving also patients' adherence.

However, considering the narrow therapeutic range of lithium, ranging from 0.60-0.80 mmol/L, with the option to reduce it to 0.40-0.60 mmol/L in case of good response but poor tolerance, or to increase to 0.80-1.00 mmol/L in case of insufficient response and good tolerance [11,134], it is necessary to accurately personalize lithium therapy. Furthermore, the appropriate clinical management of patients receiving lithium treatment should include the regular checking of serum levels and monitoring of thyroid and renal functioning. It is necessary to consider that the serum concentrations may change due to alteration in the levels of hydration, of renal functioning and/or other pharmacological interactions [131–133].

Furthermore, lithium can be used also in special population – such as elderly people or people with substance use disorder – taking carefully into consideration the side effects and the tolerability profile [26,139,140,143–148,150–156,157].

Lithium is a pharmacological agent recommended as first-line treatment for patients with bipolar disorder, during different stages of the disorder. It is time to dismiss the definition of lithium as the 'forgotten drug.' This has been mainly due to the lack of adequate training of early career psychiatrists on the specific subtle of lithium treatment. Lithium represents an essential strategy in the armamentarium of medical doctors and psychiatrists, considering also the availability of new formulation – such as the ones with – which have further improved the tolerability of the drug and patient's adherence to treatments.

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ORCID

Gaia Sampogna http://orcid.org/0000-0002-9547-2793
Gianluca Serafini http://orcid.org/0000-0002-6631-856X
Gabriele Sani http://orcid.org/0000-0002-9767-8752
Andrea Fiorillo http://orcid.org/0000-0002-6926-0762

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