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REVIEW ARTICLE

Putative Mechanisms of Action and Clinical Use of Lithium in Children and Adolescents: A Critical Review

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Abstract: ***Background*:** Lithium is a first-line treatment for bipolar disorder in adults, but its mechanism of action is still far from clear. Furthermore, evidences of its use in pediatric populations are sparse, not only for bipolar disorders, but also for other possible indications.

***Objectives*:** To provide a synthesis of published data on the possible mechanisms of action of lithium, as well as on its use in pediatric samples, including pharmacokinetics, efficacy, and safety data.

***Methods*:** Clinical trials in pediatric samples with at least one standardized measure of efficacy/effectiveness were included in this review. We considered: i) randomized and open label trials, ii) combination studies iii) augmentation studies iv) case series including at least 5 patients.

***Results*:** Different and non-alternative mechanisms of action can explain the clinical efficacy of lithium. Clinical studies in pediatric samples suggest that lithium is effective in managing manic symptoms/episodes of bipolar disorder, both in the acute phase and as maintenance strategy. Efficacy on depressive symptoms/phases of bipolar disorder is much less clear, while studies do not support its use in unipolar depression and severe mood dysregulation. Conversely, it may be effective on aggression in the context of conduct disorder. Other possible indications, with limited published evidence, are the acute attacks in Kleine-Levin syndrome, behavioral symptoms of X-fragile syndrome, and the management of clozapine- or chemotherapy- induced neutropenia. Generally, lithium resulted relatively safe.

***Conclusions*:** Lithium seems an effective and well-tolerated medication in pediatric bipolar disorder and aggression, while further evidences are needed for other clinical indications.

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1. INTRODUCTION

Lithium has been the first pharmacological agent proven to be useful in the treatment of mood disorders [1], and it is still widely used for several psychiatric disorders in adults and youths. A long lasting stream of research showed its effectiveness in adult mood disorders, with an effective protection against both depression and mania in the context of bipolar disorders, and against the risk of suicide [2, 3]. In children and adolescents, lithium has been approved by most Regulatory Agencies (including the Food and Drug Administration and the European Medicine Agency) for the treatment of bipolar disorders, although only few studies supported its efficacy in this age range [4, 5]. In the last years, new data are emerging regarding the clinical use of lithium in youth with bipolar disorder [5], as well as in other neuro-

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psychiatric conditions, but, to date, they are still sparse. A previous meta-analysis [5] on the treatment of pediatric mania was quite inconclusive in regard to lithium, as no double-blind data was available at that time (more promising results were demonstrated for second generation antipsychotics).

Studies on the mechanism of action of lithium are also quite inconclusive [6], but new frontiers, such as neuroprotective/anti-apoptotic properties, are rising [7]. The glycogen synthase kinase 3 beta enzyme (GSK3β) is now recognized as a fundamental interactor at the crossroads of metabolic and functional regulations in neurons; moreover, the actions of lithium on cell proliferation and synaptic structuring may be involved in the processes of long term potentiation or long term depression at cellular level, linked with phases of bipolar cycling [8-10]. Furthermore, some recent papers highlighted the direct effect of lithium on the white matter volume/ microstructure [11, 12].

Aim of the present paper is twofold. First, we reviewed the possible mechanism of action of lithium, in the light of recent research (*i.e*. neuroprotective/anti-apoptotic). Second, we systematically reviewed and summarized all clinical studies in youth population, spanning across clinical conditions, in order to provide the most updated and comprehensive view on the topic.

2. METHODS

We performed a Medline search from January 1980 up to the end of March 2017. Search terms were: children/ adolescents and lithium, restricted on humans, and in English language; studies without abstract were not further considered; additional manual search was performed through the references of the included papers. Irrespective of diagnosis or indications, we included all the perspective studies (of whichever duration), with children or adolescents, with homogeneous diagnosis, and with clear and standardized efficacy or effectiveness outcome measures. Augmentation trials were included only when the added value of lithium was clearly defined (*e.g*., adding lithium to partial or non-responders); combination trials were included only when it was clear that at least one arm or one time period of treatment was with lithium alone. We excluded retrospective chart reviews, case series including less than 5 patients, studies whose outcome was somewhat vague or not clearly replicable, articles reporting post hoc or mediation/moderator analyses only, as well as reviews and meta-analyses.

We firstly found 1289 articles. On the basis of title and abstract screening (if papers clearly did not fit our inclusion or exclusion criteria), results were restricted to 82 articles. Two independent authors went through the full text of these papers, analyzing the inclusion and exclusion criteria, with a third author when discrepancies occurred, until consensus was reached. Finally, 32 papers were included. The PRISMA flow chart of procedures leading to included/ excluded studies is reported in Table **1**. In the text, results from the systematic part will be organized according to the clinical indications. Levels of evidence for treatment efficacy or lack of efficacy were assessed using the Oxford Centre for Evidence-based Medicine's Levels of Evidence I [13]. Level 1a corresponds to a systematic review with homogeneity of RCTs; Level 1b corresponds to an individual RCT with a narrow confidence interval; 2a refers to an SR with homogeneity of cohort studies; 2b refers to an individual cohort study, including low-quality RCTs (*e.g*. <80% follow-up); 3a refers to an SR with homogeneity of case–control studies; and 3b refers to an individual case–control study; 4 refers to case-series.

2.1. Putative mechanisms of Action

2.1.1. Lithium is a Competitor of Magnesium

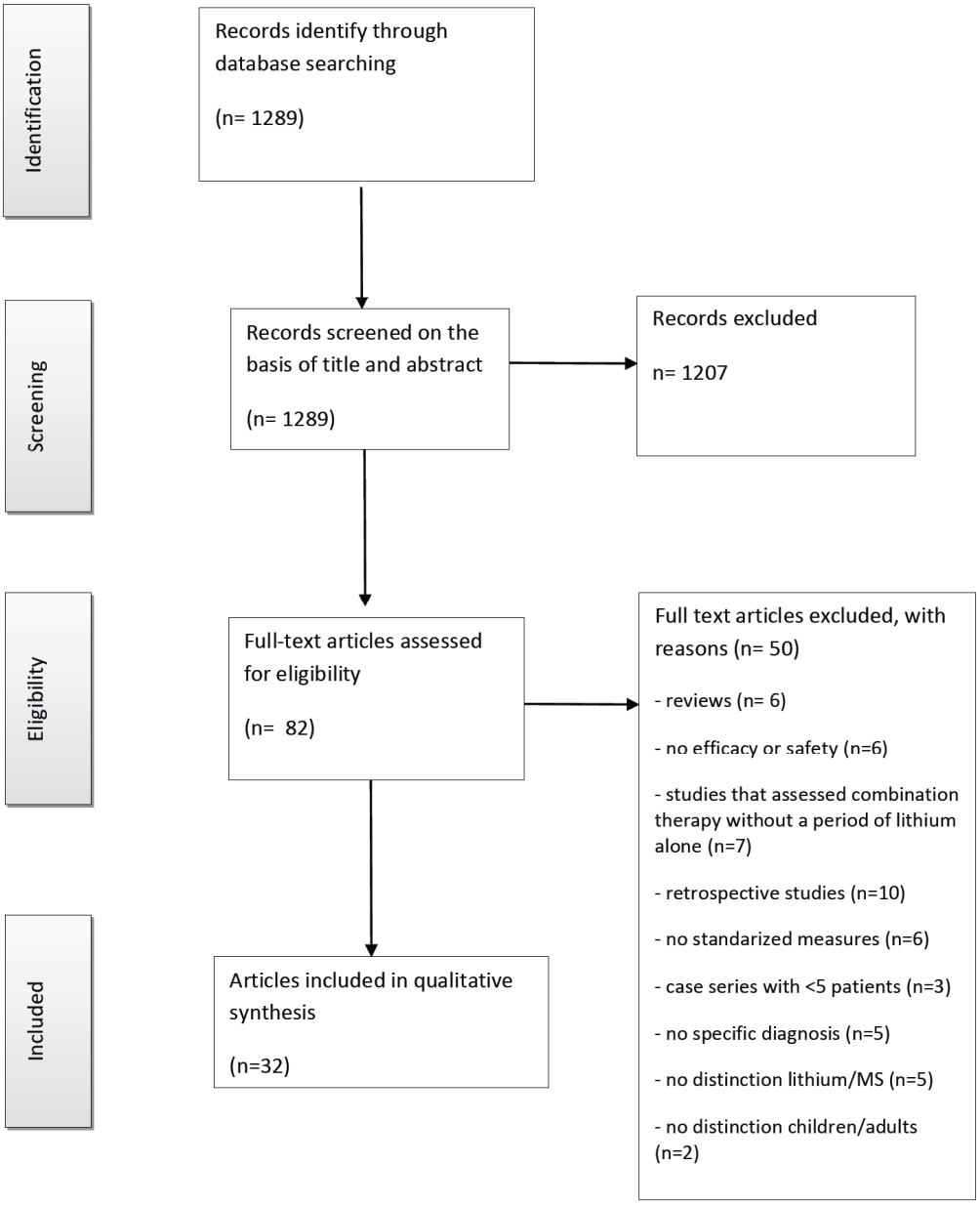
The effects of lithium seem to stem partly from the physical-chemical compatibility with magnesium ions (Mg^{2+})[14], which are essential cofactors of biological reactions involving phosphorylation. This action is involved in the regulation of the energetic metabolism, in the intracellular signal transduction pathways, and in the stabilization of macromolecular complexes. The wide potential implications of this basic mechanism of action may explain the role of lithium as a multimodal drug, with possible multiple indications. As in all competitions, magnesium is a crucial determinant of lithium activity, since the pharmacological actions of lithium depend on the reciprocal Li^{+}/Mg^{2+} concentration ratio. Among the experiments exploring the lithium-magnesium competition, the first compared the activity of lithium on the inhibition of GSK3β, described later, depending on magnesium concentrations. In the presence of 12.5 mM magnesium, lithium showed an IC_{50} of 2.5mM and an IC_{90} of 32mM. However, as the cellular content of free magnesium is lower, around 0.6-1.3 mM [15], the experiment was repeated at decreasing concentrations of magnesium, down to 1.56 mM, that is in the physiological range. In the presence of this magnesium concentration, lithium showed an IC_{50} of 0.8mM and an IC_{90} of more than 8mM [16]. These results are consistent with the therapeutic range of lithium in humans, which is between 0.4 up to 1.2mM; at maximal therapeutic doses, lithium may therefore reach a 60-80% inhibitory activity on GSK3β, depending on the local availability of free magnesium.

The role of magnesium, in the context of bipolar and other psychiatric disorders and of lithium treatment, is highly debated and controversial. Whereas magnesium levels have been described higher among bipolar patients, compared with healthy controls [17, 18], there are also studies reporting no differences [19]. One small clinical trial investigated the use of magnesium supplementation for bipolar patients, with an efficacy comparable to lithium in half cases [20]. Therefore, even if the molecular characterization of lithium as a competitor of magnesium is solid, clinical evidence is not comparably clear as regards competition with magnesium.

2.1.2. Lithium "Stabilizes" the Phosphatidylinositol-phosphate Cycle

The phosphatidylinositol-phosphate cycle is a crucial convergence step for several signal transduction pathways, centered on the regulation of calcium-calmodulin-dependent kinases and phosphatases. This cycle is based on shifts in the phosphorylation state of inositol, which can be supplied to the cell as myoinositol, or generated from glucose *via* phosphoglucomutase, or, most importantly in quantitative

Table 1. PRISMA diagram. Preferring reporting items for systematic reviews and meta-analyses.



terms, continuously recycled from other intermediates. While evidence supporting the activity of lithium on the myoinositol transporter [21] and on phosphoglucomutase is scant and conflicting [22], more consistent are data on two of the enzymes involved in regenerating myoinositol, that is inositol polyphosphate 1-phosphatase (IPP), and inositol monophosphatase (IMP). Both these enzymes require magnesium as a cofactor, and both are inhibited by lithium [23, 24]. In the absence of their activity, the phosphatidylinositol-phosphate cycle is impaired or halted, leading to a depletion of phosphatidylinositol-4,5,diphosphate (PIP_2). The PIP_2 serves as the substrate for two major signaling pathways, phospholipase C (PLC) and phosphatidylinositol-3 kinase (PI3K) (Fig. **1**). The relevance of this depletion is widely proven in animal models. One exploratory clinical trial studied the effect of an inositol-depleting diet on the efficacy of concomitant lithium treatment in patients with bipolar disorder, finding consistent clinical improvements which were attributed to the synergistic effect of diet and lithium treatment [25].

The impairment of the PLC pathway is achieved by the reduction of inositol-triphosphate (IP_3) and diacylglycerol (DAG) levels. The IP_3 acts by binding intracellular membrane receptors located on the endoplasmic reticulum, where calcium is stored: upon binding, calcium is released into the cytosol, where it can activate calmodulin-dependent protein kinases (CaMKI, CaMKII and others) and phosphatases (PP2A or calcineurin and others), involved in the regulation of a multitude of signals, including protein-kinases C (PKC) and B (Akt), and all their downstream targets. DAG may in

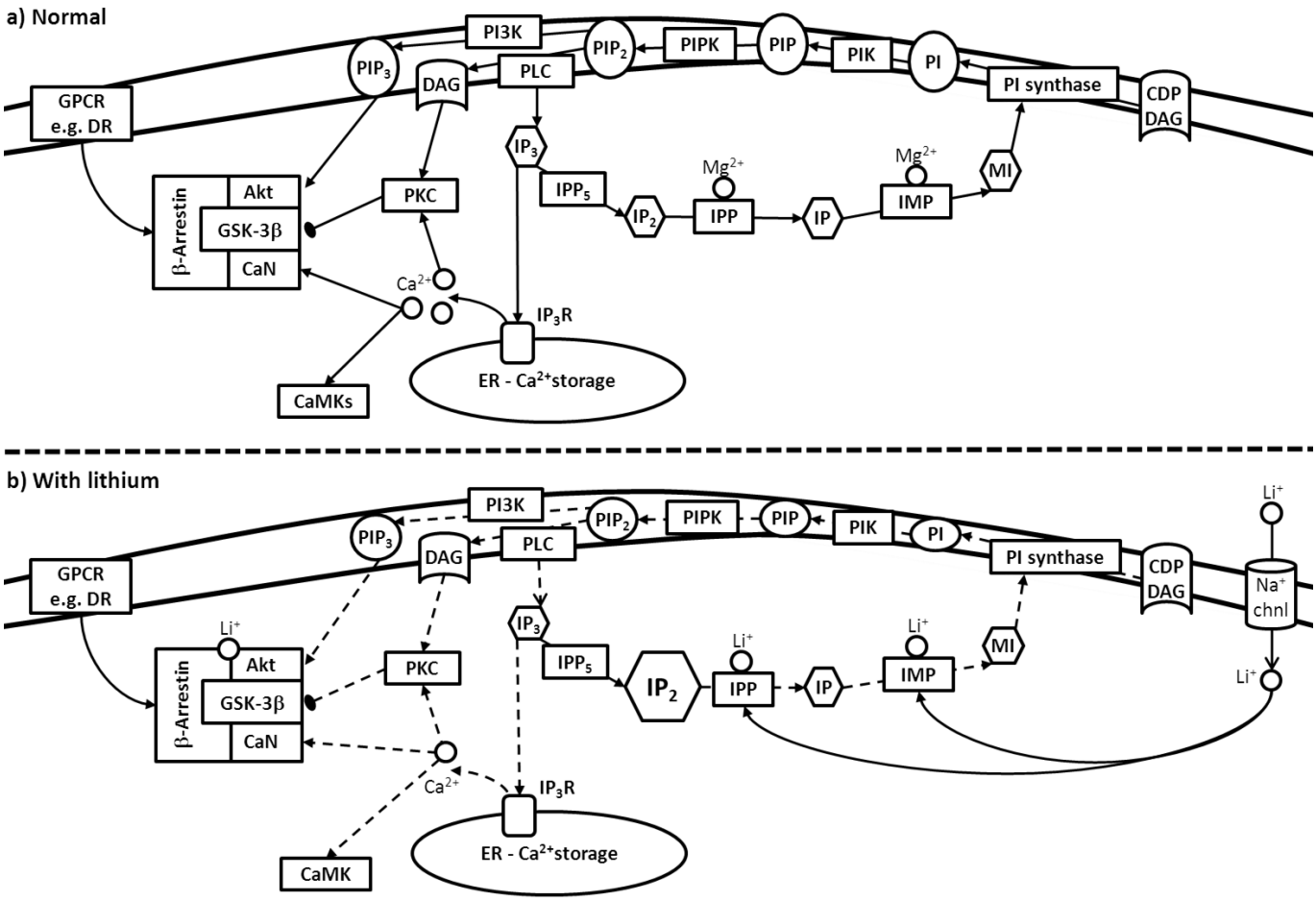


Fig. (1). Basic mechanisms of lithium function. Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions. **a**) In the absence of lithium, myo-inositol (MI) and cytidine-diphosphate-diacylglycerol (CDP-DAG) are converted by phosphatidylinositol synthase (PI synthase) into phosphatidylinositol (PI). Phosphatidylinositol-kinase (PIK) converts it to phosphatidylinositol-phosphate (PIP), which is further phosphorylated by phosphatidylinositol-phosphate-kinase (PIPK) to phosphatidylinositol-diphosphate (PIP_2). Phosphatidylinositol-diphosphate can be processed by two separate pathways. The pathway of phospholipase C (PLC) splits it to produce inositol triphosphate (IP_3) and diacylglycerol (DAG). Inositol triphosphate can be recycled by inositol-phosphate phosphatase 5 (IPP5), which converts it to inositol diphosphate (IP_2). Inositol diphosphate can be subsequently dephosphorylated to inositol phosphate (IP), by inositol phosphate phosphatase (IPP): this is a magnesium-dependent and chain-limiting step, that may impair the whole inositol-phosphate cycle. Inositol phosphate can finally be dephosphorylated by inositol monophosphate phosphatase (IMP) to regenerate myo-inositol: this is also a magnesium-dependent chain-limiting step. Before being recycled, inositol triphosphate can bind to inositol triphosphate receptors (IP_3R) on the endoplasmic reticulum, to promote the liberation of calcium into the cytosol. This free calcium rapidly binds to several proteins, among which calmodulin can promote the activation of calcium-dependent kinases (CaMKs) and phosphatases (CaN); calcium can also bind and activate protein kinase C (PKC), together with diacylglycerol. The pathway of phosphatidylinositol 3 kinase (PI3K) instead produces phosphatidylinositol-triphosphate, which can directly bind and activate protein kinase B (Akt). These pathways converge, together with the contribution from G-protein coupled receptors (GPCR) which also comprise dopamine receptors (DR), to determine the activation status of the Akt/Glycogen synthase kinase 3 beta (GSK-3β) complex. GPCRs can recruit β-arrestin, which serves as a scaffold; phosphatidylinositol-triphosphate activates Akt; protein kinase C inhibits GSK-3β; the calcium-dependent phosphatase instead activates GSK-3β. Therefore, in the absence of lithium: the inositol-phosphate cycle can be activated, calcium signals can be activated; the Akt/GSK-3β complex can be regulated. **b**) lithium can enter the cell through sodium channels (Na^+ chnl). With lithium, the magnesium-dependent and chain-limiting steps of the inositol-phosphate cycle are blocked, with the result of an accumulation of inositol-diphosphate and a depletion of all other intermediates. This causes a deactivation of both PI3K and PLC pathways, resulting in a dramatically decreased calcium signaling. Finally, the Akt/GSK-3β complex does not receive any more regulating phosphorylations or dephosphorylations; moreover, lithium can destabilize the complex.

turn trigger PKC activation, either independently or in synergy with calcium.

The impairment of the PI3K pathway is achieved by the reduction of PIP_2, which serves as the substrate for PI3K, leading to the production of PIP_3; PIP_3 in turn starts the activation chain of Akt.

Overall, the activity of lithium can be summarized through the removal of signals mediated by calcium, PKC

and Akt from the physiological control exerted by the inositol cycle. This event results in reduced responsiveness to external stimuli, and therefore in a stabilization of the calcium levels, and of the phosphorylation-dephosphorylation dynamics [26, 27]. Since several neurotransmitters act through G-protein coupled receptors (GPCRs – including several dopamine and serotonin receptors) by influencing the inositol cycle, the effect of lithium may translate into a modification or lack of response to neurochemical stimuli, which may result in the stabilization of basic and superior neurological functions.

2.1.3. Lithium "Stabilizes" the Balance between Akt and GSK3β in Favor of Akt

Increasing evidence supports the notion that lithium-dependent inhibition of the inositol cycle is based not only on a stabilization, with less responsiveness, but also on a shift of the balance towards Akt activation. As discussed above, although lithium decreases the calcium and PI3K-driven activation of Akt, a number of observations reported an increase in Akt activation and Akt-mediated effects. This is a direct effect of lithium, based on its competition with magnesium, which disrupts a balanced mechanism of reciprocal inactivation between Akt and GSK3β. This competition is physiologically activated when GPCRs are subject to endocytosis as a consequence of signaling. The internalized receptor recruits and activates a β-arrestin protein, that serves as a scaffold, and allows the interaction of proteins that would not be otherwise able to interact. In this specific case, β-arrestin2 can recruit three proteins that are capable of reciprocal inactivation: Akt, GSK3β and PP2A [28]. In this complex, PP2A can activate GSK3β and inactivate Akt, while outside of this complex Akt can inactivate GSK3β [29] (Fig. **2**). In physiological conditions, GPCR activation can influence the activity of PP2A, and thus the balance between Akt and GSK3β: High GPCR internalization/calcium signaling may decrease Akt activity while low internalization may decrease GSK3β activity.

Interestingly, whereas PP2A is under the indirect control of lithium (*via* inhibition of calcium-calmodulin), the kinase activity of GSK3β on Akt is also inhibited directly by lithium, because GSK3β requires magnesium as a cofactor [30]. Moreover, the entire complex requires magnesium for its structural stabilization, and lithium interferes with the assembly of phosphorylated Akt with β-arrestin2 [31]. These actions of lithium point to activation of Akt and the inactivation of GSK3β.

Therefore, lithium removes the Akt/GSK3β balance from the control of GPCRs and calcium signals, and at the same time changes the functional significance of the inositol cycle inhibition, leading to the preservation of peculiar phosphorylated forms of Akt (active) and GSK3β (inactive). By this activity, lithium acts as a "biased" stabilizer. Both Akt and GSK3β are predominantly known for their activity in other contexts, however several among their targets are relevant to the survival, proliferation and function of neurons.

2.1.4. The Role of Lithium for Neuronal Function and Mental Health, Through Akt

Akt stimulates cell survival in two complementary ways, *i.e.* inhibiting apoptosis and promoting cell cycle progres-

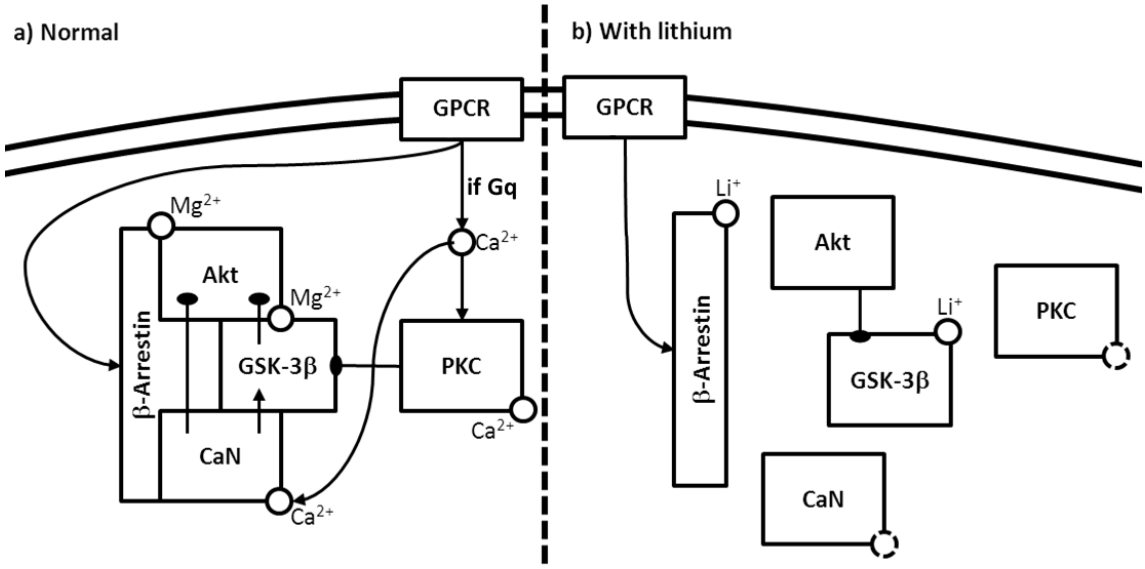


Fig. (2). Basic mechanisms of lithium effects on the Akt/GSK-3β complex. Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions. **a**) In the absence of lithium, the activation of G-protein coupled receptors (GPCRs) can lead to the activation of αq G-protein subunits that stimulate an increase of cytosolic calcium levels and activate protein kinase C (PKC) and the calcium-dependent phosphatase (CaN). While protein kinase C can inhibit glycogen synthase kinase 3 beta (GSK-3β), the calcium-dependent phosphatase can inhibit protein kinase B (Akt) and activate GSK-3β. Magnesium has additional roles since it can stabilize the Akt/GSK-3β complex and it is a cofactor required for the activity of GSK-3β. Therefore, in the absence of lithium, the Akt/GSK-3β promotes the inactivation of Akt and the activation of GSK-3β. **b**) with lithium, calcium signals are suppressed, leaving PKC and CaN inactive. Moreover the Akt/GSK-3β complex cannot be stabilized and GSK-3β is deprived of its required cofactor. This leaves Akt as the only active enzyme with the result of additional GSK-3β inhibition.

sion, which may also promote neurogenesis in the adult brain and resilience against traumas or neurotoxic insults (Fig. **3**) [32, 33]. Akt may also strengthen neurons through an increased capability of protein transcription and translation [34, 35]. This is coupled to actions on the energetic metabolism, where the inhibition of GSK3β, hexokinase2 and phosphofructokinase2 shifts the energetic balance towards glycolysis; the increase in glucose consumption with less mitochondrial engagement may provide protection against oxidative stress and excitotoxicity [36-38].

Akt phosphorylates and activates β-catenin, a transcription factor crucial for the survival, proliferation and differentiation of adult neural stem cells (depending on the presence of co-factors [39]). Indeed, impairment in Akt signaling is widely reported in animal models of neuronal deficits, as well as in patients with schizophrenia, who were reported to show decreased Akt activation and reduction in left hippocampal volume [40]; to date, no data in this respect are available regarding bipolar patients. Another contribution of Akt to neuronal survival may come from the activation of the cyclic AMP responsive element binding factor (CREB), through the Raf pathway, which leads to increased production of brain-derived neurotrophic factor (BDNF) [41, 42]. A study on bipolar patients and healthy controls identified elevated but erratic levels of circulating BDNF in patients, together with reduced grey matter volumes; controls instead displayed greater grey matter volumes and lower BDNF levels that resulted to be inter-correlated [43].

The importance of BDNF levels is underlined by other studies, reporting that in bipolar patients the methylation levels (implying lower transcription) of BDNF correlated with the presence of a depressive phase, an effect reversible by lithium treatment [44]. A similar observation related low levels of BDNF in depressive, but also in manic phases in bipolar patients, again reversible by lithium treatment; this study also showed that plasma levels of lithium and BDNF were inter-correlated [45]. Similarly, BDNF levels have been proposed as both predictors [46] and markers of lithium treatment efficacy [47], where higher baseline and stimulated levels associate with a better therapeutic response.

Besides survival and proliferation, Akt can also influence the intracellular transport dynamics by acting on the Rac pathway [48], with possible effects on memory consolidation [49]. Another debated target of Akt in neurons is NF-kB [50], as NF-kB may control by post-transcriptional actions some aspects of postsynaptic membrane structuring, by clustering together with glutamate receptors and increasing their membrane density, which is involved in potentiation mechanisms [51, 52]. Akt can also exert rapid influences on neuronal functioning, by phosphorylating several neurotransmitter receptors (such as specific NMDA glutamate receptor subunits [53]), although the precise function of such modifications in the context of a complex spectrum of activations and inactivation (PKA, PKC, calcium), and of concomitant neurotransmitter activities, is still a matter of debate [54]. Indeed, oscillations of the transcription levels of Akt have been reported in patients, who displayed low Akt during depressive episodes, which recovered after lithium treatment and in connection with clinical improvement [55].

2.1.5. The Role of Lithium for Neuronal Function and Mental Health, Through GSK3 β

GSK3β can be viewed as a functional antagonist of Akt in several regards (Fig. **4**). For instance, it decreases the activity of CREB, and particularly reduces BDNF levels, it phosphorylates β-catenin, and improves its proteolytic degradation. Two studies conducted in psychiatric patients (schizophrenic or with major depression) suggested a connection between homozygosis for the *major* frequency allele of an intronic GSK3β polymorphism, and reduced cortical grey matter, possibly mediated by the association with lower β-catenin levels [56, 57]. This apparently puzzling finding can be explained since the minor frequency allele, associated to a reduced function of GSK3 β, should associate with improved basal health of neurons. Indeed, controversial [58] investigations of another polymorphism (rs334558) of GSK3 β found that patients carrying homozygotic minor frequency alleles (*i.e.* impaired GSK3 β) had larger grey matter volumes [59, 60], better white matter integrity [61], and they responded better than others to lithium treatment [62]. The aspect of brain connectivity (as investigated through diffu-

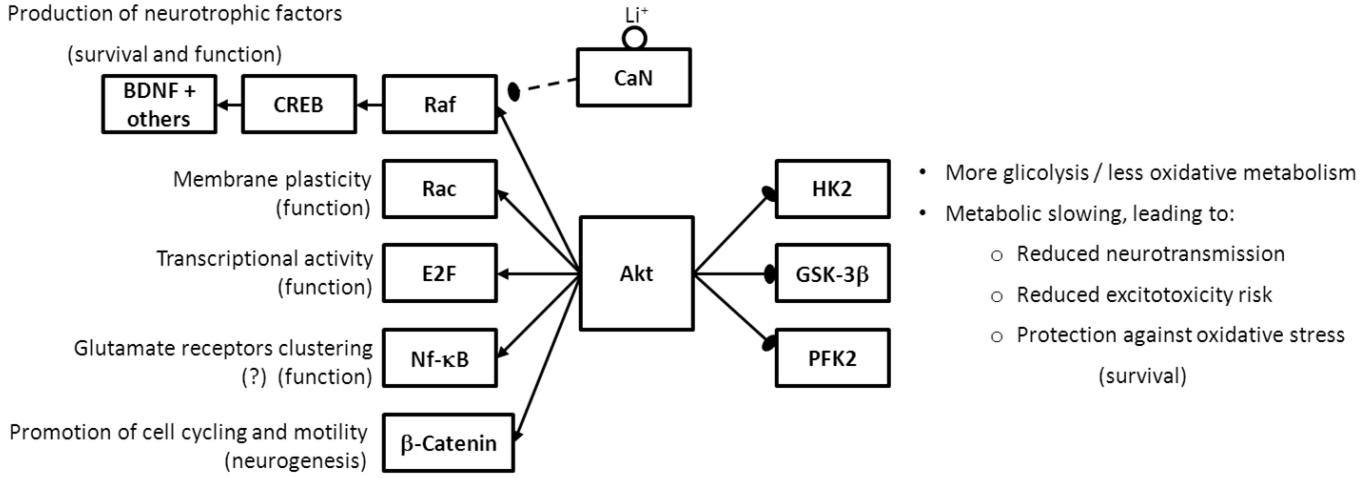


Fig. (3). Relevant effects of Akt activation. Boxes show proteins targeted by Akt. Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.

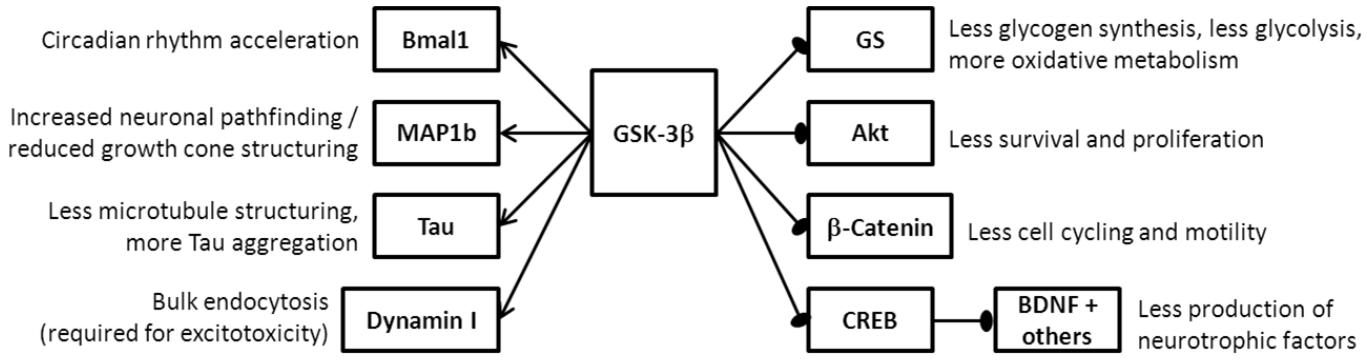


Fig. (4). Relevant effects of GSK-3β activation. Boxes show proteins targeted by GSK-3β. Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.

sion tensor imaging) seems to be crucial for the etiopathogenesis of bipolar disorders, and patients often display connectivity issues, which can be reverted by long-term lithium treatment [63, 64]. Again, related to neuronal structure and functions, GSK3 β can phosphorylate Dynamin 1, an event required in order to perform bulk endocytosis [65]. This is an endocytosis mechanism only elicited when cells have to face a massive rate of membrane recycling. This event is among those sustaining the excessive neuronal activation and neurotransmitter release involved in excitotoxicity. GSK3 β can also phosphorylate Tau, possibly leading to disrupted vesicle trafficking and formation of Tau fibril aggregates [66]. GSK3 β also phosphorylates MAP1b, promoting axonal pathfinding and the emergence of multiple growth cones, in spite of cone growth and structuring [67]. Another peculiar activity of GSK3 β, demonstrated in striatal neurons, is the phosphorylation of the transcription factor Bmal1; this event allow its degradation, thereby promoting an accelerated cycling of circadian rhythms [68]. Indeed, among bipolar patients, circadian rhythms are dysregulated towards an excessively rapid cycling, which possibly contributes to the disorganization of brain connectivity [69]. Overall, the inhibition of GSK3 β may promote cell survival and differentiation, BDNF production, it may prevent excitotoxicity and the disorganization of the neuronal cytoskeleton, favoring cone growth and synaptic structuring; moreover it can slow down the circadian rhythm. Observations in patients indirectly link the GSK3 β activity status with the bipolar phase cycling: a longitudinal study monitored at several time points the blood levels of inactivated GSK3 β, finding a correlation between higher inactivation and the predominance of depressive phases, as opposed to manic phases, where GSK3 β was mostly active. Interestingly, euthymic phases were associated with average levels of inactive-GSK3 β, that however were still lower than those observed in control subjects [70]. This observation is supported by other investigations, linking low activation levels of GSK3 β with depression phases of bipolar disorders, however low GSK3 β activity does not seem to be related with affective traits in healthy controls [71]. These observations would favor the role of lithium as an anti-manic drug, with possible depressant actions in bipolar patients.

2.1.6. Lithium and PKA, Still an Open Question

Whereas the influence of lithium on the calcium, PKC and Akt pathways is quite well defined, it is not known whether the effect of lithium on the levels of cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase (PKA) is direct or indirect. It has been speculated that, since the production of cAMP by adenylyl cyclase (AC) is magnesium dependent, lithium may directly inhibit AC and cAMP formation [72]. Studies that reported an in-vitro inhibition of AC by lithium often used toxic concentrations of lithium, being questionably relevant in a clinical perspective. However, it is well known from preclinical evidence that manganese, another ion that can compete with magnesium, can bind to AC, and directly activate it [73]. This supports the importance of ion cofactors for AC activity, although data are only preclinical. In fact, it is not really known whether lithium increases or decreases cAMP, as this action seems to be highly dependent on the context, such as the brain region [74, 75]. A detailed investigation on rats showed that after lithium treatment, cAMP increased in the frontal cortex only, while it decreased in the neostriatum, and remained unchanged in the hippocampus, hypothalamus, thalamus, amygdala and cerebellum [76]. Part of these apparent inconsistences may depend upon the expression of different AC isoforms, and it becomes clearer in view of the finding that hypofunctional ADCY2 (the gene coding for AC isoform 2) polymorphic variants associated with a diagnosis of bipolar disorder [77]. A possible explanation is that, while most of the experiments conducted *in vitro* evaluated the interplay between lithium and AC1, the isoform most widely expressed in the human brain is AC2, which is insensitive to a series of stimuli that trigger or inhibit AC1, *i.e.* α_s and α_i subunits of GPCRs. This may imply that lithium may activate (or at least not-inactivate) the cAMP-PKA system in a brain-region-wise manner, further contributing to the inhibition of GSK3 β and promotion of Akt activity (also through the PKA-mediated inhibition of PP2A) [78], while in other brain areas lithium may inhibit the generation of cAMP, blunting its own effect on the GSK3β/Akt interplay, while still subtracting it from the control by α_s and α_i GPCRs. This activity may also be interpreted as a means of "biased stabilization", through which lithium may selectively increase and decrease the activity of different brain areas.

2.1.7. Data from Studies Including Children and Adolescents

As mentioned above, lithium interacts with the phosphoinositide cycle. Looking at studies investigating the neural

effect of lithium in an adolescent population, two studies are worth mentioning. The first [79] demonstrated changes in brain proton spectra and in myoinositol levels in 11 children with bipolar disorder compared with 11 controls. Patients received a proton magnetic resonance spectroscopy (^{1}H MRS), and a procedure of single voxel placement (2x2x2 cm^3) in anterior cingulated cortex was performed in order to collect the ^{1}H spectra at the baseline and after acute treatment (7 days). Authors found a significant reduction of the myoinositol/creatinine ratio in brains of children and adolescents with bipolar disorder after seven days of lithium treatment. This result may represent a possible pathway towards the identification of a biological marker of response to lithium therapy in youth [79]. Conversely, Patel *et al*. [80] did not find significant changes of myoinositol levels in the prefrontal cortex of 28 adolescents with bipolar disorder I (current depressed episode) after acute (7 days) and chronic (42 days) lithium treatment (30 mg/Kg). This inconsistency may be due to the different phases of the disorder in which patients were tested, but it warrants further *in vivo* and human studies in order to elucidate the neural mechanism of action of lithium.

2.2. Pharmacokinetics

A critical element of lithium administration is to start therapies with a dose high enough to induce a fast response, while remaining below the toxicity threshold. This approach is feasible nowadays, by virtue of studies that initially identified plasma levels associated with fixed lithium doses, and subsequently succeeded to predict weight-adjusted lithium doses necessary to obtain defined plasma levels. We here summarize papers published on pharmacokinetics including selectively children and adolescents. Vitiello *et al*. (1988) firstly described the drug pharmacokinetics in children (age range 9-12 years) with conduct or adjustment disorders receiving 300 mg/day of lithium, generally finding similar parameters as compared to adults, except for the elimination half-life and total clearance, which were faster in children [81]. Malone *et al*. then followed the method of Cooper and colleagues [82, 83] to predict which lithium doses could lead to plasma concentrations in the therapeutic window of 0.6 – 1.2 mEq/L in 16 children and adolescents with conduct disorder (13 M, 3 F; age range 9-17; mean age: 12.7, SD: 2.1). The procedure included a pre-treatment administration of 600 mg of lithium, after which patients received 600 mg/day for two days, then increased by 300 mg/day until the individual predicted maintenance dose was reached. The dose was then kept for six days to ensure steady–state. The predicted doses ranged from 600 to 1.800 mg/day, and serum concentrations from 0.58 to 1.13 mEq/L; no adverse effects occurred. The Authors concluded that the method of Cooper and colleagues was useful to manage lithium administration in children and adolescents. Later, the Collaborative Lithium Trials (CoLT), a pediatric study with multiple aims and phases, provided results on post-acute effectiveness, dosing strategies and first-dose lithium pharmacokinetics in children with bipolar disorder I [84-86]. In particular, Findling *et al*. found that a starting dose of 300mg/day for subjects weighing less than 30 kg, or of 300 mg, 2 to 3 times/day, for subjects weighting 30Kg or more, was appropriate in a sample of 39 subjects (20 M, 19 F, mean age: 11.8yy) with current manic or mixed states. Authors concluded that the initial dosage should be carefully evaluated, based on the body weight [85]. Landersdorfer *et al* extracted detailed pharmacokinetics and pharmacodynamics data from the CoLT population (children and adolescents with age range 7-17 years). They built a study model that accounted for inter–individual variability (IIV), lean body weight (LBW) and total body weight (TBW). Results showed that a daily dose of 25 mg/kg TBW was the best among the evaluated regimens. This posology, that corresponded to an average of 1337 mg/day in their sample, attained a reduction in YMRS to <15 and a CGI improvement of 1 or 2 points in 70% patients, moreover in 74% of the patients, this dose achieved a 50% reduction of baseline YMRS. Scaling by TBW was a correct strategy for patients in a normal weight range (TBW and body composition), whereas authors suggested to scale by LBW for overweight and obese patients to avoid adverse effects, since lithium mainly distributes into non–fat tissues. Pharmacokinetic parameters were in line with those of adults for patients scaled to 70 Kg TBW: total body clearance = 1.59 L/h/70kg TBW (adults: 1.32-2.15 L/h/70Kg TBW); distribution volume at steady state (V_{ss}, $V_{central}$+V_{periph}) = 56.1 L/70 Kg TBW (adults: 38.6-70.2 L/70 Kg TBW), and terminal half – life = 29h (adults: 13.8-29h) [86].

2.3. Efficacy of Lithium in Children and Adolescents

2.3.1. Bipolar Disorder (Manic, Hypo-manic, Mixed Episodes-Depressive Symptoms)

Fourteen studies explored the efficacy of lithium in bipolar disorders, the majority of them focused on both children and adolescents. Results are summarized in Table **2**. We here briefly describe each study, starting from the most recent.

Fallah and collagues [87] recently reported on a RCT comparing lithium+placebo and lithium+tamoxifen (based on the possible PKC inhibition effect of tamoxifen) in decreasing acute manic symptoms. Both groups showed a reduction in the Young Mania Rating Scale (YMRS) [88], and an improvement in the Children's Depression Inventory (CDI) scores, with a greater improvement in the arm with tamoxifen. The study is novel and intriguing, but some methodological shortcomings (*i.e*., small sample size, lack of examining comorbidities) require caution and replication.

The Treatment of Early Age Mania (TEAM) study is a multicenter, prospective, randomized, masked comparison of divalproex sodium, lithium carbonate, and risperidone in an 8-week parallel clinical trial. A total of 279 children and adolescents with DSM-IV diagnosis of bipolar I disorder, mixed or manic episode, aged 6 to 15 years. were enrolled. Several studies from the same dataset [89-91] are available in the literature. In the first study [89], authors reported a clear superiority in the response rate, assessed by Clinical Global Impression-for Bipolar Illness Improvement-Mania, of risperidone over both lithium (68.5% vs 35.6%; $\chi 2$ 1=16.9, P<.001) and divalproex sodium (68.5% vs 24.0%; $\chi 2$ 1=28.3, P<.001), while lithium and divalproex sodium did not differ each other. Secondary outcomes (Kiddie Mania Rating Scale, Children Global Assessment Scale [CGAS], absence of mania diagnosis) were all consistent with the primary analysis. In the other study [90], depressive symptoms (assessed with Clinical Global Impression Bipolar Depression)

Table 2. Summary of reviewed study: focus on efficacy and safety.

Author/Year	N° of Patients	Age	Metodology and Duration	Daily Doses and/ or Serum Level of Lit	Measures	Main Results	Founders
Bipolar spectrum (Bipolar I, II, NOS maniac/hypomanic/mixed/depressive phases)							
Fallah *et al*., 2016 [81]	N=44 (n=22, n=22)	9-20 ys	RCT (Lit+PLB or Lit+tamoxifen) 4 weeks	Serum level 0.8-1.1 mg/L	YMRS, CDI	Both groups improved with Tamoxifen+Lit group showing an increased rate of improvement (reduction in YMRS and slight decline in CDI scores)	Isfahan University of Medical Sciences
Salpekar *et al*., 2015 [84]	N=279[1] (n=90, n=89, n=100)	6-15 ys	Multicenter RCT (Val, Lit or Risp) 8 weeks	Serum level 1.1-1.3 mEq/L	CGI, CGAS, CDRS-R	Depressive symptoms improved with all 3 medications, Risp yield more rapid improvement than Lit or Val	NIMH grants
Findling *et al*., 2015 [86]	N=81(n=53, n=28)	7-17 ys	Multicenter DBRPCT 8 weeks	Mean dose 1500 mg/d; serum level 0.98+/-0.47 mEq/L	YMRS, CGI-I, CDRS-R, CGAS	Lit was effective in reducing manic symptoms (response criteria 32%, remission criteria 26%); significant increase in thyrotropin level in Lit compared with placebo	NIH
Walkup *et al*., 2015 [85]	N=154[1]	6-15 ys	Multicenter RCT (Val, Lit or Risp) 8 weeks	Serum level 1.1-1.3 mEq/L	CGAS, KMRS, CGI-BP-IM	Switching to Lit (or Val) resulted less effective than switching to Risp. Response rate to Risp 47.6% vs Lit 12.8% and Val 17.2%	NIMH grants
Findling *et al*., 2013 [88]	N=41[2]	7-17 ys	Open label 16 weeks	Mean dose 1470.7 mg/d; serum level 1.0 mEq/L	YMRS, CGAS, CGI, CDRS-R	Lit was safe and effective in long term treatment; no substantial symptom improvement during continuation phase	Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.
Geller *et al*., 2012 [83]	N=279[1] (n=89, n=90, n=100)	6-15 ys	Multicenter RCT (Val, Lit or Risp) 8 weeks	Serum level 1.09 mEq/L	CGI-BP-IM, KMRS	Response rate of Risp group 68.5% vs Lit group 35.6% and Val group 24.0%; weight gain and prolactin levels significantly greater with Risp.	NIMH grants
Findling *et al*., 2011 [87]	N=61[2]	7-17 ys	Open label, dose-based RCT 8 weeks	Mean dose 1500 mg/d; serum level 1.05 mEq/L	K-SADS, YMRS, CDRS-R, CGI-S, CGI-I, CGAS and others*	61.7% ≥ 50% improvement in YMRS score, 58,3% achieved response, 71,7% not remission. Lit was well tolerated. All the three treatment arms had similar effectiveness, side effect profiles, and tolerability.	Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.
Patel *et al*., 2006 [74]	N=27	12-18 ys	Open label 6 weeks	Serum level: 1-1.2 mEq/L	CDRS-R, CGI, YMRS, KSADS, CGAS	Response rate 48% and remission rate 30%. Lit was well-tolerated.	A Klingenstein Third Generation Foundation grant and an NIMH grant
Findling *et al*., 2005 [89]	N=60 (n=30, n=30)	5-17 ys	DBRCT (Val or Lit) 76 weeks	Serum level: 0.6 -1.2 mEq/L	K-SADS, CGI-I, CGI-S, CGAS, YMRS, CDRS-R	No difference in time to recurrence of symptoms between the Lit and Val monotherapy groups	Stanley Medical Research Institute primarily, in part NIMH Developing Centers for Interventions and Services Research.

(Table 2) contd….

Author/Year	N° of Patients	Age	Metodology and Duration	Daily Doses and/ or Serum Level of Lit	Measures	Main Results	Founders
Bipolar spectrum (Bipolar I, II, NOS maniac/hypomanic/mixed/depressive phases)							
Kafantaris *et al*., 2004 [91]	N=40 (n=19, n=21)	12-18 ys	DBR discon-tinuation trial 2 weeks	Mean serum level 0.99 mEq/L	K-SADS, YMRS, CGI S, CGAS, HAM-D, GCJ	No difference in exacerbation rates between Lit group (52.6%) and placebo group (61.9%)	US Public Health Service
Kafantaris *et al*., 2003 [90]	N=100	12-18 ys	Open label 4 weeks	Mean dose 1355 mg/d Serum level 0.93 mEq/L	K-SADS, CGI-I, CGAS, YMRS, HAM-D	Response rate to Lit 55%, 46% required adjunctive antipsy-chotic medication, remission rate 26%, Lit was well-tolerated.	US Public Health Service
Kafantaris *et al*., 2001 [92]	N=10(n=5, n=5)	12-18 ys	Open label 4 weeks	Serum level: 0.6-1.2 mEq/L	YMRS, BPRS, HAM-D	3/5 non psychotic subjects were responders to Lit monotherapy; 0/5 psychotic subjects re-sponded to Lit monotherapy, 5/5 were responders to Lit+Hal	US Public Health Service
Kowatch *et al*., 2000 [93]	N= 42 (n=13, n=13, n=15)	8-18 ys	Open label, randomized (Lit, Val, CBZ), 6 weeks	Mean dose about 30 mg/kg/day; serum level: 0.8-1.2 mEq/L	CGI-BP, CGAS, YMRS	Response rate >50% in YMRS score, large ES for all 3 medica-tions, ES for Lit=1.06, response rate Lit=38%	NAMI/Stanley Foundation Re-search Awards Program and NIMH grants
Geller *et al*., 1998 [94]	N=25 (n=13, n=12)	12-18 ys	DBRPCT, 6 weeks	Mean dose 1769 mg/d	CGAS, mood items of K-SADS	Response rate: 46.2% for Lit vs 8.3% for placebo. Lit was well-tolerated.	National Inuitute on Drug Abuse
Strober *et al*., 1998 [95]	N=60 (n=30*, n=30) * prior history of adhd	13-17 ys	Open label, 4 weeks	Mean dose 600-900 mg/d; serum level 0.9-1.5 mEq/L	BRMS, CGI	Manic adolescent with child-hood ADHD had less improve-ment compared to a control group (without pre existing ADHD); response rate 86,7% vs 66,7%	Not reported
Strober *et al*., 1990 [96]	N=37	13-17 ys	Open label discontinuation trial, 18 months	Serum level 0.79 mEq/L	CGI, HAM-D, MSRS	Relapse rate 56.8%; relapse among non-completers was three times higher (92.3%) than for completers (35.5%)	NIMH grants
Unipolar Depression/Severe mood dysregulation							
Dickstein *et al*., 2009 [97] (Severe mood dys-regulation)	N=25 (n=14, n=11)	7-17 ys	DBRPCT, 6 weeks	Serum level 0.8-1.2 mEq/L	CGI, PANSS, YMRS, CGAS, CGI, CDRS-R, MRS	Not significant differences in either clinical or MRS outcome measures between groups	NIMH grants
Geller *et al*., 1998 [99]	N=30 (n=13, n=17)	6-12 ys	DBRPCT, 6 weeks	Serum level 0.99+/- 0.16 mEq/L	9 items K-SADS, CGAS	Both groups significantly im-proved, but Lit was not signifi-cantly more efficacious than placebo	NIMH grants
Strober *et al*., 1992 [100]	N=24	Mean age 15.4 ys	Open label augmentation trial, 3 weeks	Serum level 0.89 mEq/L	HAM-D, CGI	42% of patients treated with Lit showed clinical response vs 10% of the controls; the mean degree of improvement was similar between augmented and controls (both statistically sig-nificant); the addition of Lit was generally well tolerated	Not reported

(Table 2) contd….

Author/Year	N° of Patients	Age	Metodology and Duration	Daily Doses and/ or Serum Level of Lit	Measures	Main Results	Founders
Conduct Disorder (with or without ADHD)							
Malone *et al*., 2000 [102]	N=40 (n=20, n=20)	10-17 ys	DBRPCT, 6 weeks	Dose range 300-2100 mg/d; serum level 0.8-1.2 mEq/L	Diagnosis according to DSM III criteria, DISC, GCJCS, CGI, OAS	Lit safe and effective for reducing aggression, Lit group 80% responders vs placebo group 30%responders	US Public Health Service
Rifkin *et al*., 1997 [106]	N=33 (n=17, n=16)	12-17 ys	DBRPCT, 2 weeks	Serum level 0.6-1 mEq/L	DISC, OAS, BRS, CTRS, HRS, ADD/H Adolescent Self Report Scale	1/12 (8.3%) patients taking placebo and 3/14 (21.4%) taking Lit met remission criteria (no statistically significant)	NIMH grants
Campbell *et al*., 1995 [103]	N=50 (n=25, n=25)	5-12 ys	DBRPCT, 6 weeks	Dose range 600-1800 mg/d, mean dose 1248 mg/d; serum level 0.53-1.79 mEq/L	GCJS, CGI, CPRS, CTQ, POMS, diagnosis according to DSM III criteria	Lit superior to placebo in severe aggression	US Public Health Service, NIMH; Hirschell and Deanna E. Levine Foundation, the Marion O. and Maximilian E. Hoffman Foundation, Inc. and Beatrice and Samuel A. Seaver Foundation
Malone *et al*., 1994 [105]	N=8	9.2-16.9 ys	Open label, 4 weeks	1200-1800 mg/day, 1350 mg/day(mean dose), serum Lit level 1,12 mEq/L	Diagnosis according to DSM III-R criteria, OAS, GCCR	Patients taking Lit presented a significant improvement in OAS and GCCR	Child and Adolescent Mental Health Academic Award from NIMH
Carlson *et al*., 1992 [109]	N=11	5,11-12,10 ys	DBRPC crossover trial, 8 weeks	Mean dose 600-1500 mg/d, serum level 0.7-1.1 mEq/L	CDRS, MRS, CPT, MFFT, PAL	3/10 improved enough to be discharged on Lit; Lit less effective on aggressive behaviour that exist independently of BD	Not reported
Campbell *et al*., 1984 [108]	N=61 (n=20, n=20, n=21)	5.2-12.9 ys	DBRCT (Lit or Hal) 6 weeks	Mean dose 1166 mg/d, serum level 0.9 mEq/L	Diagnosis according to DSM III-R criteria, CPRS, CGI, CPRS, CTQ, GCJ	Lit and Hal were statistically superior to placebo in reducing aggression; Hal was associated with more frequent AE than Lit	Public Health Service grant, NIMH
Hematological Use							
Mattai *et al*., 2009 [124] (Clozapine-Induced Neutropenia)	N=7	6,7-14,8 ys	Open label, duration unspecified	Dose 450-1500 mg/d	ANC	ANC increased significantly in six out of seven patients (by a mean of 66%)	Not reported
Steinherz *et al*., 1983 [122] (Chemotherapy-induced myelosuppression)	N=231 (n=79, n=71, n=63)	1-21 ys	RCT augmentation trial (Lit or Lit+Oxy) duration unspecified	Serum level 0.2-1.4 mEq/L	WBC count	Lit reduced the period of neutropenia after chemiotherapy, the addiction of Oxy improved appetite and weight; 91% of the control group became severely neutropenic vs 80% of Lit group and 78% of Lit+Oxy group	National Cancer Institute Grant and the Smith, Kline and French Laboratories

(Table 2) contd….

Author/Year	N° of Patients	Age	Metodology and Duration	Daily Doses and/ or Serum Level of Lit	Measures	Main Results	Founders
Hematological Use							
Chan *et al*., 1981 [123] (Neutropenia associated with various chronic conditions)	n=5	1.5-6 ys	Case series, 30-50 days	Serum level 0.1-1.0 mEq/L	CFU-C, CAS	Lit increases CAS and CFU-C in two patients, one with normalization of neutrophils	Medical Research Council of Canada and by Phisicians Services Incorporated Foundation
Steinherz *et al*., 1980 [121] (Chemotherapy-induced leukopenia)	N=78 (n=39, n=39)	3-26 ys	Open label controlled trial, approximately 14 days	Serum level 0.2-1.2 mEq/L (median 0.7 mEq/L)	WBC count	Lit reduced significantly the degree of leukopenia after, 15% of patients in the treatment group experienced side effects which disappeared with drug discontinuation	National Cancer Institute and the Smith, Kline and French Laboratories
Genetic diseases							
Leu-Semenescu *et al*., 2015 [112] (KLS)	N=130 (n=71 of which 40 children, n=59)	21,1+/-9,6 ys	Open label, controlled study 21.5 +/- 17.8 months	Serum level 0.8-1.2 mEq/L	Frequency and duration of episodes, time incapacitated	Mean and longest duration of episodes and time incapacitated significantly decreased in the Lit group. After Lit 36.6% had no more episodes vs 3.4% of patients with no Lit. Mild AE	Hospital Clinical Research Program from the French Health Ministry and Assistance Publique-Hôpitaux de Paris.
Berry-Kravis *et al*., 2008 [116] (Fragile-X Syndrome)	N=15	6-23 ys	Open label, 2 months	Serum level 0.8-1.2 mEq/L	ABC-C, CGI, VABS, VAS, RBANS, ERK activation time	Lit had positive effects on behavioral/adaptive skills, and single cognitive measure; reduction of activation time of ERK; no serious AE	Grant fron FRAXA Research Foundation (EBK) and the Spastic Paralysis Research Foundation of the Illinois- Eastern Iowa District of Kiwanis International
Poppe *et al*., 2003 [111] (KLS)	N=5	13-17 ys	Case series, max 36 months	Serum level 0.6-0.9 mEq/L	Polysomnography (EEG, EOG, EMG, pulse oxymetry, elector-cardiogram), MRI, Frequency and duration of episodes	Lit reduced duration and frequency of episodes in KLS, no significant side effects, MRI was normal in all five patients	Not reported

Abbreviations: Drugs: Lit: Lithim; Val: Divalproex Sodium; Risp: Risperidone; CBZ: Carbamazepine; Hal: Haloperidol; Oxy: oxymetholone; PLB: placebo Study design: DBRCT: double blind randomized controlled trial; RCT: randomized controlled trial; DBRPCT: double blind randomized placebo controlled trial Psychometric Measures: ABC-C: Aberrant Behavior Checklist-Community Edition; ACTeRS: ADD-H Comprehensive Teacher's Rating Scale; BRMS: Bech-Rafaelsen Mania Scale; BPRS: Brief Psychiatric Rating Scale; BRS: Behavior Rating Scale; CAT: Concept Attainment Task; CDI: Child Depression Inventory; CDRS-R: Child Depression Rating Scale Revised; C-GAS: Children Global Assessment Scale; CGI-S: Clinical Global Impression of Severity; CGI-I: Clinical Global Impression-Improvement; CGI-BP-IM: Clinical Global Impression-Bipolar-Improvement Mania; CPRS-CP: Conners Parent Rating Scale; CPT: Continuous Performance Test; CTQ: Conners Teacher Questionnaire; CTRS: Conners Teacher Rating Scale; DISC: Diagnostic Interview Schedule for Children; DOTES: Dosage Record and Treatment Emergent Symptoms; GCCR: Global Clincal Consesus Rating; GCJCS/GCJS: Global Clinical Judgments (Consensus) Scale; HAM-D/HRS: Hamilton Rating Scale for Depression; IGRS: Inpatient Global Rating Scale; K-PAL/PAL: Kingsbourne's computerized version of the Paired Associated Learning Paradigm; KMRS: K-SADS Mania Rating Scale; K-SADS: Kiddie-Schedule for Affective Disorders and Schizophrenia; MFFT: Matching Familiar Figures Test; MSRS: Manic State Rating Scale; OAS: Over Aggression Scale; PANSS: Positive and Negative Syndrome Scale; PMT: Proteus Maze test; POMS: Profile of Mood States ratings; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RT: Reaction Time task; ST: Stroop Test; STRM: Short -term recognition Memory test; TESS: Treatment Emergent Symptom Scale; VAS: Visual Analog Scale; VABS: Vineland Adaptive Behavior Scale; WISC-R: Wechsler Intelligence Scale for Children Revised; YMRS: Young Mania Rating Scale *ARS-IV: attention-deficit/hyperactivity disorder Rating Scale-IV; CMRS-P: Child Mania Rating Scale-Parent; CSQ: Caregiver Strain Questionnaire; Family Environment Scale; Drug Use Screening Inventory; IDA: Irritability, Depression and Anxiety Scale; NCBRF-TIQ: Nisonger Child Behavior Rating Form-Typical IQ Version; PARS: Pediatric Anxiety Rating Scale; The Social Adjustment Inventory for Children and Adolescents; PGBI-10M: Parent General Behavior Inventory-10 Item Mania Scale. Laboratory Test and others: WBC: White Blood Cell ANC: Absolute Neutrophil Count; CFU-C: Granulocyte precursors (Colony Forming Unit in Culture); CSA: Colony Stimulating Activity; ERK: Extracellular signal-regulated kinase; EEG: electroencephalogram; EMG: electromyography; EOG: electroculogram; MRI: Magnetic Resonance Imaging; MRS: Magnetic resonance spectroscopy; AE: Adverse events; KLS: Klein Levin Syndrome; NIH: National Institute of Health; NIMH: National Institute of Mental Health. 1 same dataset, Walkup 2015 comprised a subset of patients from Geller 2012 that were deemed as partial or non responder. 2 same dataset, Findling 2013 comprised a subset of patients from Findling 2011 that were deemed as responder or partial responder.

showed greater improvement with risperidone, whereas similar improvement with all the three medications resulted from assessment with Child Depression Rating Scale, as well as for suicidality (assessed with the item 13 of CDRS). Also, risperidone appeared to yield more rapid improvement than lithium or divalproex sodium [90]. Another study from the same dataset [91] explored the effect of switching or adding one of the other anti-manic drug in partial or non-responder of the main study. Switching to lithium (or divalproex) resulted less effective than switching to risperidone. The trial was multicentric, well designed and well powered, yielding reliable results.

Findling and colleagues [92] conducted the first double blind, placebo- controlled trial, including 81 outpatients aged 7 to 17 years. Lithium was superior to placebo in reducing manic symptoms (assessed by YMRS) with a Cohen's d effect size of 0.53. Results also favored lithium on CGI-Improvement, whereas no differences were reported for CDRS and CGAS (secondary measures). The study has some noteworthy strengths, but it is slightly limited in duration and sample size. Two other studies are available, reporting data from the same project [93, 94]. In the first study [93], an 8-week, dose-based randomized, open label trial, based on a reduction of ≥ 50% of CGI-S and YMRS scores, an improvement as found in 70% and 61% of the patients, respectively. Also, a fast titration did not determine a worse safety profile. In the second study [94], a long-term, open label trial, including responders or partial responders of the first study, responders maintained their stabilization over the long term, whereas the partial responders did not experience further improvement, despite the opportunity to receive adjunctive medications.

An open trial examined the efficacy of lithium for the treatment of acute depression in adolescents with bipolar disorder [80]. This was a 6-week study involving 27 adolescents (mean age= 15.6±1.4 years). The mean CDRS decreased significantly from baseline to endpoint, with a large effect size (d=1.7). Using a ≥50% reduction in baseline CDRS scores as the primary effectiveness measure, the authors reported a response rate of 48% and a remission rate of 30%. The study is limited by the open label design and the small sample size, although the dropout rate was low.

In 2005, Findling and colleagues explored the comparative effectiveness of lithium and divalproex in the maintenance treatment of juvenile bipolar disorder, over 76 weeks [95]. Patients who stabilized their symptoms for 4 consecutive weeks with a combination of lithium and divalproex were randomized the monotherapy (divalproex or lithium alone), and followed up to 76 weeks. Time to mood relapse or study discontinuation did not differ between the two groups (log-rank [1 df] = 0.35, p = 0.55). Similarly, Kafantaris *et al*. [96] reported the results of a large open trial that served as the lead in study to a randomized placebo-controlled discontinuation study, which is described below [97]. In the open trial, 100 youth with bipolar disorder type I (mean age= 15.23 years) were treated with lithium for a duration of 4 weeks (mean serum level of 0.93± 0.21 mEq/L). Forty-six subjects received concomitant antipsychotic medication for associated psychosis or severe aggression. Using a reduction of ≥ 50% in baseline YMRS score as response criterion, the response rate was 55%, with a large effect size for change in manic symptoms (d = 1.48).

The randomized, placebo-controlled, discontinuation follow-up phase of the same study was a 2-week trial that involved 40 subjects (mean age=15.16±1.72 years), who had previously responded to the open-label lithium treatment. In this trial, 19 subjects continued on lithium monotherapy, while 21 subjects received placebo. No statistically significant differences were found in exacerbation rates between the two treatment groups (52.6% and 61.9, respectively), suggesting that a 4-8 week treatment with lithium monotherapy may not be adequate to maintain remission of mood symptoms. Studies are well conducted, but they allowed a concomitant antipsychotic use, then results are hard to interpret in regard to lithium alone. In fact, in a small study from the same research group [98], when five patients who started with a combination of lithium and haloperidol discontinued haloperidol, a relapse of psychotic symptoms was apparent within 1 week, despite the ongoing treatment with lithium.

Kowatch *et al*. [99] compared the efficacy of lithium, divalproex sodium and carbamazepine (CBZ), randomly administered for 6 weeks to 42 outpatients (mean age 11.4 years) with a diagnosis of bipolar spectrum disorder. The effect size (determined from the change in baseline to endpoint of YMRS scores) for lithium was 1.06 with a response rate (reduction of ≥ 50% in baseline YMRS score) of 38%, not statistically different from divalproex sodium and CBZ. The study is of interest because it allows comparison within three drugs, but it is relatively small and unblinded.

Geller *et al*. [100] explored in a prospective, placebo controlled trial, the efficacy of lithium monotherapy in 25 adolescents (mean age= 16.3±1.2 years) with a history of bipolar disorder I or II, or major depressive disorder (MDD) associated with one predictor of future bipolar disorder (*e.g*., switching during treatment with a tricyclic antidepressant), and comorbid substance dependency disorder. After a randomization to a 6-week treatment with either lithium or placebo, 46.2% of the subjects significantly responded with lithium, compared to 8.3% with placebo. The improvement was significant using both categorical and continuous outcome measures, and for symptoms of both mania and substance abuse. The study is unique in assessing the comorbid condition, but the small sample size, the exclusion of suicidal adolescents and the short duration may limit the results.

The possible moderator effect of prior ADHD diagnosis on the response to lithium in manic patients was firstly explored by Strober *et al*. [101]. Thirty youths with acute mania and prior history of ADHD were compared with an age- and sex-matched patients with acute mania and no premorbid history of ADHD (age range=13 – 17 years). Both groups presented a decrease in Beck-Rafaelsen Mania Scale (BRMS), but the improvement was greater in non-ADHD patients. Furthermore, the median time of onset of sustained response was also shorter (17.0 days) for the non ADHD group compared to the prior ADHD group (23.0 days).

Strober *et al*. [102] reported on 37 adolescents with bipolar mania stabilized with lithium, naturalistically followed up

for 18 months. Thirteen patients did not complete the follow up on lithium (mean time on lithium 3.92 months). At the end of the follow-up period, 21 patients (56,8%) relapsed, and the relapse rate was three times higher among patients who discontinued lithium earlier. The naturalistic design reflects the real world practice, but raises a possible allocation bias.

In summary, there is level 1b evidence that lithium treatment is effective in pediatric mania; there is not level 1b evidence that lithium is effective in ameliorating depressive symptoms, but some studies are highly suggestive, providing level 2b evidence. Some long term studies are also available and support its use in relapse prevention.

2.3.2. Severe Mood Dysregulation

Dickstein *et al*. [103] assessed the efficacy and safety of lithium in youth with severe mood dysregulation (SMD) [104], a new clinical diagnosis close to the disruptive mood dysregulation disorder, included by DSM 5 within the category of Depressive Disorders. Forty-five patients participated, but 20 were not randomized due to a significant clinical improvement during the placebo run-in phase, so 25 SMD patients, aged 7 to 17 years, entered the 6 weeks, randomized, double blind trial (14 on lithium, 11 on placebo). No significant between-group differences in clinical outcomes (CGI-I and Positive and Negative Syndrome Scale factor 4 score -sum of excitement, hostility, uncooperativeness, poor impulse control, other secondary outcomes) were detected (effect size= 0.23). The study has some strengths (placebo run-in phase, associated magnetic resonance spectroscopy study supporting the clinical findings), but the number of the randomized patients is very small.

In summary, there is Level 1b Evidence that Lithium is not Effective in Severe Mood Dysregulation.

2.3.3. Unipolar Depression

Lithium was also evaluated by Geller *et al*. [105] for the treatment of Major Depressive Disorder (MDD) in 30 prepubertal children (6-12 years) with a family history of bipolar disorder (80%) or a multigenerational family history of MDD without bipolar disorder (20%) in a 6-week, double-blind, placebo controlled trial. No significant differences between groups were detected on both continuous and categorical outcomes (CGAS, score at 9 items of K-SADS).

2.3.4. Lithium as Augmenting Medication

Augmentation with lithium was assessed in a 3-week, open label study [106] in 24 youth non-responders after 6 weeks of treatment with imipramine, compared with 10 controls who did not receive lithium augmentation. In the lithium group, 42% of the patients showed evidence of clinical improvement, compared to 10% of the controls; the mean degree of improvement, assessed with Hamilton Depression Rating Scale (HAM-D) [107] was similar between augmented and controls (both statistically significant), and modest in magnitude (reduction of about 14 % of HAM-D score in both groups).

In summary, there is level 1b evidence that lithium is not effective alone in unipolar depression; an open label study (level 2b) suggests that it may be useful as add-on treatment in some non-responders to antidepressants.

2.3.5. Conduct Disorder/aggression

Malone *et al*. [108] conducted a 6-week (the first two as placebo run-in), double-blind, randomized, placebo controlled study including 40 patients with conduct disorder, aged from 10 to17 years. Lithium was statistically and clinically superior to placebo (odds ratio of 9.3 to be a responder in lithium group; 80 % of responders in the lithium group, compared to 30% in the placebo group), using several categorical and continuous measures (Global Clinical Judgement Consensus Scale (GCJS), CGI and Overt Aggression Scale (OAS) [109, 110]. The same research group [111] previously conducted a small open label trial (4 weeks, 8 patients), supporting the clinical usefulness of lithium, based on OAS and CGI.

On the contrary, in a shorter (2 weeks), single blind, placebo-controlled trial, lithium showed no advantage when compared with placebo in 33 adolescent inpatients with conduct disorder. At the completion of the study, only 1 of 12 patients taking placebo and 3 of 14 taking lithium met remission criteria [112]. The study had a 1-week placebo run in phase, but it is too short to provide conclusive and reliable results.

Campbell *et al*. [109] reported a 6-week, double-blind, randomized, placebo-controlled trial in 50 children aged 5 to 12 years with chronic and treatment resistant aggressiveness in the context of a conduct disorder diagnosis. The study had 2 additional weeks of a placebo run-in phase. Lithium was superior to placebo on several measures (Children's Psychiatric Rating Scale (CPRS), GCJS, CGI); no effect of lithium was detected on Profile of Mood States ratings (POMS) [113]. In a previous study from the same research group with a similar population and design, 61 children were randomly assigned to haloperidol, lithium or placebo for a 4-week double blind trial. Lithium and haloperidol were both statistically and clinically (GCJS) superior to placebo in reducing aggression, without differences between them [114]. Finally, in another small trial of 11 patients, children treated per a minimum of 8 weeks, lithium carbonate resulted effective in improving self-control, aggression and irritability [115].

In summary, there is level 1b evidence that lithium treatment is effective to treat aggression in the context of conduct disorder; all studies, however, are highly limited by small sample sizes and short follow-ups.

2.3.6. Kleine-Levin Syndrome

Kleine-Levin syndrome is a clinical condition characterized by a symptomatological triad of recurrent hypersomnia (mandatory for the diagnosis), with or without hyperphagia, and/or hypersexuality. Perceptual abnormalities and behavioural dyscontrol are common. An incomplete presentation of KLS is more common than the presence of the complete triad, and it can resemble many psychiatric conditions [116]. Poppe and colleagues [117] reported the clinical course of five adolescents with KLS who were treated with lithium. All patients had relapses during lithium treatment, but the treatment was associated with shorter episodes of mono-

symptomatic hypersomnia without other co-occurring behavioural symptoms. Statistical modelling showed that the risk of relapsing under lithium dropped from 100 % to 93 % per month of therapy, and that the maintenance of lithium shortened the mean duration of episodes to 19 %. Furthermore, the treatment was well tolerated. Leu-Semenescu and colleagues [118] compared the benefits and risks of lithium therapy *vs*. abstention / other treatments in a prospective, open-label, controlled study in 130 patients with KLS. Seventy-one patients (including 40 children) were treated with lithium (median dose 1,000 mg/day); 49 subjects did not receive medications, 5 were on valproate, and 5 were on the contraceptive pill. The characteristics of the disorder (frequency, mean, and longest durations of episodes, time incapacitated per year) were compared before and after follow-up in the lithium vs no-treatment group. The patients were followed up for a mean of 21.5 ± 17.8 months. Compared to the untreated patients, patients receiving lithium presented a decrease of the duration of the longest episode (-18 ± 35 vs -5 ± 13 days), of the time spent incapacitated (-37 ± 65 vs -10 ± 38 days), and of the frequency of episodes per year (-2.6 ± 2.9 vs 1.3 ± 2.78 episodes). Side effects were reported by 50% of the patients in the lithium group, but they were mild, and included tremor, increased drinking, diarrhoea, and subclinical hypothyroidism. In this large study, the benefit/risk ratio of lithium therapy was reported superior to that of abstention. In conclusion, in KLS with a high frequency of episodes and severe behavioural changes, lithium represent a favourable treatment option, as evidences suggest (with level 2b evidence) that it can decrease frequency and duration of the episodes.

2.3.7. Fragile X Syndrome (FXS)

Fragile X syndrome (FXS) results in a loss of Fragile X mental retardation protein (FMRP) expression, and characteristically presents with intellectual disability and a characteristic behavioural profile that includes autism spectrum disorder, ADHD, sensory hypersensitivity, hyperarousal, and anxiety [119]. Abnormal neurodevelopment is thought to result from the epigenetic silencing of FMR1 and the consequent absence of its protein product, influencing glutamate signalling, memory, and regulation of the critical serine/threonine regulatory kinase, glycogen synthase kinase-3 (GSK-3) [120].

Lithium treatment has been studied extensively in both mouse and fruit fly models of FXS, and it has been shown to reverse numerous behavioural, physiological, cellular, and molecular phenotypes [121]. In humans, Berry-Kravis *et al* [122] conducted a pilot add-on trial to evaluate the safety and efficacy of lithium, titrated to levels of 0.8-1.2 mEq/L, in 15 individuals with FXS, ages 6-23. The primary outcome measure was the Aberrant Behaviour Checklist-Community Edition (ABC-C) Irritability Subscale [123] and secondary outcome measures were other ABC-C subscales, clinical global improvement scale (CGI), visual analogue scale for behaviour (VAS), Vineland Adaptive Behaviour Scale (VABS), [124], exploratory cognitive and psychophysiological measures and an extracellular signal-regulated kinase (ERK) activation assay [125]. These measures were administered at baseline and after 2 months of lithium treatment. Side effects were quantified with a standardized checklist and lithium blood level, complete blood count (CBC), thyroid stimulating hormone (TSH), and chemistry, at the baseline, after 2 weeks, 4 weeks and 2 months [122]. The only significant treatment-related side effects were polyuria/polydipsia (n = 7) and elevated TSH (n = 4). Although the ABC-C Irritability Subscale showed only a trend toward improvement, there was significant improvement in the Total ABC-C score ($p = 0.005$), VAS ($p = 0.003$), CGI ($p = 0.002$), VABS Maladaptive Behaviour Subscale ($p = 0.007$), RBANS List Learning ($p = 0.03$), and an enhanced ERK activation rate ($p = 0.007$), although several exploratory tasks were too difficult for lower-functioning FXS subjects. Results from this study are consistent with results in mouse and fly models of FXS, and suggest that lithium is well tolerated, and may provide functional benefits in FXS, possibly by modifying the underlying neural defect [122]. In summary, results from a pilot study showed promising results for the use of lithium in Fragile-x syndrome, but evidences are still limited (level 4).

2.3.8. Haematological Uses of Lithium

Lithium carbonate produces neutrophilia and increases circulating CD34+ cells of marrow origin [126]. Lithium increases G-CSF (Granulocyte Colony-Stimulating Factor), and augments G-CSF effects. In bone marrow transplantation, pre-harvest lithium-assisted hematopoietic stem cell mobilization may be useful as well [126]. Use of lithium during hematological investigations was considered in the 1980s, especially for the treatment of aplastic anaemia and congenital neutropenia, but no definitive use in haematology has emerged. In a first randomized trial assessing lithium in chemotherapy-induced myelosuppression [127], authors reported that lithium reduced the time period of leukopenia during which patients may acquire infections. The same group [128] reported on a trial of patients (1-21 years old) with various bone tumours such as osteosarcoma, Ewing's sarcoma, or rhabdomyosarcoma receiving oxymetholone, randomized to lithium or lithium plus oxymetholone after chemotherapy. Seventy-one patients with lithium, 63 with both drugs, and 79 in the control group, were compared. White blood cell count and neutrophil nadirs were better in both treatment groups than in the controls ($p = 0.001$), but an additive effect of oxymetholone above and over lithium alone was seen only in patients under 15 years old ($p = 0.05$). The median duration of severe neutropenia (absolute neutrophil count less than 1000/cm3) was 6.2 days/patient in the control group, but only 4.5 days/patient and 3.8 days/patient in the lithium and lithium plus oxymetholone groups, respectively ($p = 0.0001$).

Regarding chronic neutropenia, a case series of 5 patients [129] described an ameliorating effect of lithium in 2 patients, one of them with substantial and persisting normalization of neutrophil counts. No toxic adverse events occurred. Authors argued that lithium may be effective in clinical conditions where the colony-stimulating activity was low.

Based on these observations, lithium has been proposed for the treatment of clozapine-induced neutropenia. Mattai and colleagues [130] conducted a systematic audit of 7 patients with Childhood Onset Schizophrenia (COS) who developed neutropenia during clozapine treatment, in order to

explore the management of neutropenia and concomitant use of lithium to counter the neutropenia. After initiation of lithium, absolute neutrophil count (ANC) increased significantly in six out of seven subjects by 29% to 106% with a mean of 66%. In addition, six out of seven subjects continued using both clozapine and lithium for over 2 years (range: 2.0 to 7.2 years) [130].

In summary, evidences from RCT (level 2b) suggest a possible effect of lithium on some outcomes of severe haematological diseases, as well as in clozapine-induced neutropenia (level 4).

2.4. Safety of Lithium in Children and Adolescents

Long-term naturalistic studies, namely those in an active pharmacovigilance context, and dataset studies, are better suited to detect the frequency and the intensity of adverse events (above all, rare adverse events) of a specific treatment. No studies of this type are available for lithium in children and adolescents. We thus based our considerations on the safety sections of the longer or larger trials described above.

In the TEAM study, from baseline up to 8 weeks, lithium was associated with moderate weight gain (from 40.2 to 41.6 Kg), increase of calcium (from 9.5 to 9.7 mg/dl), and thyrotropin level (from 2.1 to 5.2 mUI/l), decrease of urine specific gravity (from 1021 to 1013), prolongation of electrocardiogram PR (from 127 to 140 msec) and QTc (404 to 414 msec) intervals. Compared to risperidone, the magnitude of weight gain (and other metabolic parameters such as BMI and prolactin) was lower, whereas thyroid dysfunction is specific to lithium. Adverse events that increased their frequency from baseline to at least 1 week were: abdominal pain, weight loss, weight gain, nausea, vomiting, headache, dry mouth, nasal congestion, frequent urination, enuresis, excessive thirst.

In the double-blind study by Findling *et al*. [92], no participants discontinued the study due to lack of tolerability. All the side effects involving at least 5% of participants and with a frequency at least twice than placebo were all mild to moderate in severity, namely vomiting, nausea, headache. Vomiting and nausea vanished after respectively 7.3, 14.7 days, and sometimes following a dose reduction. No statistical difference was evident between lithium and placebo with respect to weight gain. A statistically significant increase in thyrotropin concentration of 3.0 ± 3.1 mIU/L was observed in the lithium group, compared with –0.1 ± 0.9 mIU/L with placebo ($P < .001$). In the open label continuation study (16 weeks) [94], no serious adverse events were reported. The most common adverse events (at least 20% of the participants) were vomiting, headache, abdominal pain, tremor and weight gain.

In the Findling *et al*. study [95] which followed patients up to 18 months, adverse events reported by > 5 % of the 30 patients in the lithium arm were: vomiting, headache, tremor, enuresis, stomach pain, nausea, diarrhea, decrease appetite, increased thirst, upper respiratory congestion, fever, sore throat; roughly, they are similar to those reported in the valproic acid arm.

In summary, all these studies indicate that gastrointestinal symptoms (namely, vomiting, nausea, diarrhea, decrease appetite, stomach pain), urinary symptoms (frequent urination, enuresis, increased thirst), headache and tremor are relatively frequent, but they rarely require drug discontinuation. Gastro-intestinal symptoms are usually reported in the first weeks, often tend to decrease with time, but sometimes a dose reduction is needed. Increased thyreotropin level is frequent, usually with normal levels of thyroid hormones, while increased weight gain is inconstant and moderate. Cardiac effect are statistically, but not clinically significant. However, long term studies specifically designed to assess safety issues are lacking.

3. DISCUSSION

After a survey of possible mechanisms of action of lithium, and data about pharmacokinetics in youth, we have provided a critical revision of literature regarding clinical uses, efficacy and safety of lithium in children and adolescents. Insight on mechanism of action of lithium are emerging from molecular and animal studies, with new frontiers opening. Unfortunately, we are still far from elucidating the whole mechanism (from genes to molecules to neurons to behaviours), and this is more evident in children and adolescents. Myoinositol/creatinine ratio offers an intriguing perspective [79], but data are controversial [80] and limited to few studies. Interestingly, Kafantaris [12] reported a possible neural target of lithium. Adolescents with bipolar disorder showed lower functional anisotropy in left and right cingulum hippocampus compared to healthy control. After 4 weeks of lithium treatment, functional anisotropy in left cingulum hippocampus increased in responders, whereas it decreased in non-responders; also, its baseline level predicts a lower symptoms severity following 8 weeks of treatment. Studying other regions of interest, as well as other phases of the disease would enhance this very relevant area of research.

From a clinical point of view, good evidence supports the efficacy of lithium as a possible first line treatment of pediatric bipolar disorder. It appears particularly effective in acute manic phases (level 1b), as well as in the maintenance phase of the disorder, preventing relapses [89, 92]. In acute mania, second generation antipsychotics (namely risperidone) may be more effective than lithium [89], and a possible mediator of risperidone superiority may be ADHD comorbidity (both diagnosis and severity), as risperidone and lithium had a similar response rate in patients without ADHD. This is consistent with the older study by Strober *et al* [95] that revealed a poorer response of lithium in patients with a prior history of ADHD. It is possible that lithium affects specifically the mood, whereas risperidone and possibly other antipsychotics, (see also Masi *et al*. [131, 132] and Kirino [133] for quetiapine and aripiprazole) have a wider effect, on mood dysregulation, hyperactivity and impulsivity. Safety profile, namely weight gain and risk of metabolic syndrome, were more favorable with lithium.

More controversial is the efficacy of lithium on depressive symptoms of bipolar youth. Although some evidences (level 2b) suggest a possible efficacy [80, 90], others are

discouraging (level 1b for lack of efficacy) [92]. Studies from adult patients indicate a possible efficacy of lithium on suicidality [2], particularly frequent in adolescents with unipolar and bipolar mood disorders. Further studies may be able to more closely disentangle the specific effect of different mood stabilizers and antipsychotics of (hypo)manic and depressive symptoms (or phases).

Evidences supporting a possible use of lithium in unipolar depression and severe mood dysregulation are even scanter. Both the randomized controlled studies are negative [103, 105] (level 1b for lack of efficacy); the open label combination study of partial responders to Imipramine [106] showed modest results (level 2b). A possible indication of a combined antidepressant-lithium treatment, that clearly requires further investigations, may be represented by adolescents who committed suicide attempt and are still depressed, as indicated by the Treatment of Suicidal Adolescent (TASA) study [134, 135].

Efficacy of lithium in aggressive youth is supported by two old, controlled trial [108, 109] (level 1b), as well by a large retrospective study (not included in the review) [136]. Given the strong effect of lithium on impulsivity, this kind of aggression, overt, affective and impulsive, may be more sensitive to lithium, compared to the more proactive and callous aggression, as already suggested in the literature [136].

Some evidence (level 2b) support also the use of lithium in a rare, or, more precisely, rarely diagnosed syndrome, such as the Kleine Levin syndrome. Lithium may be useful in reducing the frequency and the intensity of hypersomnia, cognitive impairment, apathy episodes, and even more, in controlling emotional and behavioral dyscontrol and hypersexuality. These findings are consistent with some reviews [137, 116], indicating that lithium was useful in about 40% of patients for stopping relapses when compared to no treatment (19%).

Evidence supporting a possible role of lithium in fragile-X syndrome (level 4) needs randomized, controlled studies on larger samples, although the possible role of lithium on the underline genetic defect is potentially intriguing [122].

The use of lithium to manage neutropenia in children and adolescents assuming clozapine for Childhood Onset Schizophrenia (COS) is of relevant clinical significance. Children with COS are often treatment resistant, and clozapine may be the most effective, if not the unique, pharmacological treatment [138]. When neutropenia occurs during this treatment, lithium can represent the most effective strategy for a rechallenge, namely when alternative treatment are ineffective. However, this strategy is not without risks, and a close monitoring of these patients, for persisting of worsening neutropenia, as well as for other complications (*i.e.*, increased risk of Neuroleptic Malignant Syndrome) is warranted.

Surprisingly, despite its use in adults [139], we did not find evidence for the use of lithium in any kind of headaches in children and adolescents. Given the tolerability profile of lithium (see below), this area of research can be enhanced.

Other unexplored areas of possible utilization of lithium, such as the emotional and behavioral dysregulation, irritability and aggression of youth with intellectual disability and/or autism spectrum disorders, may be explored, namely when second generation antipsychotics are associated with metabolic side effects. A retrospective chart review (not included in this review) [140] suggests promising results, as well as a good tolerability. Again, a RCT would be welcome.

Most of the studies suggest a relatively good tolerability of lithium, namely in comparison with the well-known risks of most of the second generation antipsychotics [141, 142]. Adverse events (AE) are generally rare and mild to moderate, above all weight gain, diabetes and dyslipidemia, which, on the contrary, represent the most troublesome AE during SGA treatment [143, 144]. Also cardiac AE (*i.e.*, QTc prolongation) seem less concerning, compared to antipsychotics. Concerns about some electrocardiographic findings was raised by the TEAM study [89], but other studies did not report electrocardiographic issues, nor serious cardiac events. Monitoring of thyroid and kidney functions is mandatory, although the raise of thyrotropin concentration was generally below a frank hypothyroidism level [89]. Large naturalistic pharmacovigilance studies, as well as dataset studies on these issues are not available. Given the chronic nature of the disorders for which lithium is indicated, long-term studies addressing the safety of lithium in large populations, including thyroid, kidney and heart functioning, will be clearly welcomed. Dataset studies, that may allow to detect uncommon adverse events, are needed too.

We have provided a comprehensive review on mechanism of action and clinical data of lithium in children and adolescents. Our search strategy was limited by English language and by the publication year range (with possible exclusion of potentially significant data). However, older studies may have presented inconsistencies or vagueness of the diagnosis, or may have used unstandardized measures, resulting in unreliable or biased results.

CONCLUSION

In summary, lithium is a milestone in the treatment of various symptoms in various neuropsychiatric disorders, first of all the manic symptoms of bipolar disorders, and the impulsive aggression. Other uses are still viable options, *e.g.* to treat depressive symptoms in the context of bipolar disorders, or to manage unipolar depression in treatment resistant youth, with suicidal attempts, non suicidal self injuries or other impulsive behaviors. A re-discovery of the use of lithium in children and adolescents is desirable, based on the new insights on his mechanisms of action, on the possible role of biomarkers of efficacy, and in the light of a reassuring safety profile.

LIST OF ABBREVIATIONS

ABC-C	=	Aberrant Behaviour Checklist - Community Edition
AC	=	Adenylyl Cyclase
ACTeRS	=	ADD-H Comprehensive Teacher's Rating Scale
ADCY2	=	Adenylyl Cyclase type 2

ADHD = Attention Deficit Hyperactivity Disorder

AE = Adverse Event

Akt = Protein Kinase B

ANC = Absolute Neutrophil Count

ARS-IV = attention-deficit/hyperactivity disorder Rating Scale-IV

BDNF = Brain-Derived Neurotrophic Factor

Bmal1 = Brain and Muscle Arnt-Like protein-1

BMI = Body Mass Index

BRMS = Beck-Rafaelsen Mania Scale

BPRS = Brief Psychiatric Rating Scale

BRS = Behavior Rating Scale

CaMK = Calmodulin-dependent protein Kinases

cAMP = Cyclic-Adenosine MonoPhosphate

CAT = Concept Attainment Task

CBC = Complete Blood Count

CBZ = Carbamazepine

CDI = Children Depression Inventory

CDRS = Child Depression Rating Scale

CFU-C = Granulocyte precursors (Colony Forming Unit in Culture)

CGAS = Children Global Assessment Scale

CGI = Clinical Global Impression

CGI-S = Clinical Global Impression-Severity scale

CGI-BP-IM = Clinical Global Impression-Bipolar-Improvement Mania

CMRS-P = Child Mania Rating Scale-Parent

CoLT = The Collaborative Lithium Trials

COS = Childhood Onset Schizophrenia

CPRS = Children's Psychiatric Rating Scale

CPT = Continuous Performance Test

CTQ = Conners Teacher Questionnaire

CTRS = Conners Teacher Rating Scale

CREB = cAMP Response Element-Binding protein

CSA = Colony Stimulating Activity

CSQ = Caregiver Strain Questionnaire

= Family Environment Scale

= Drug Use Screening Inventory

DAG = Diacylglycerol

DBRCT = Double blind randomized controlled trial

DBRPCT = Double blind randomized placebo controlled trial

DISC = Diagnostic Interview Schedule for Children

DOTES = Dosage Record and Treatment Emergent Symptoms

DSM-IV = Diagnostic and Statistical Manual of mental disorders fourth edition

ERK = Extracellular signal-Regulated Kinase

FKS = Fragile X Syndrome

FMR1 = Fragile Mental Retardation 1 (gene)

FMRP = Fragile X Mental Retardation Protein

G-CSF = Granulocyte-Colony Stimulating Factor

GCCR = Global Clincal Consesus Rating

GCJS = Clinical Judgement Consensus Scale

GPCRs = G-Protein Coupled Receptors

GSK3β = Glycogen Synthase Kinase 3 beta

Hal = Haloperidol

HAM-D/HRS = Hamilton Rating Scale for Depression

IC50 = Half maximal Inhibitory Concentration

EEG = Electroencephalogram

EMG = Electromyography

EOG = Electroculogram

IDA = Irritability, Depression and Anxiety Scale

IGRS = Inpatient Global Rating Scale

IH- MRS = Proton Magnetic Resonance Spectroscopy

IIV = Inter–Individual Variability

IMP = Inositol MonoPhosphatase

IP3 = Inositol-triPhosphate

IPP = Inositol Polyphosphate 1-Phosphatase

K-PAL/PAL = Kingsbourne's computerized version of the Paired Associated Learning Paradigm

KMRS = K-SADS Mania Rating Scale

K-SADS = Kiddie-Shedule for Affective Disorders and Schizophrenia

KLS = Kleine-Levin Syndrome

LBW = Lean Body Weight

LI+ = Lithium+

MAP1b = Microtubule-Associated Protein 1B

MDD = Major Depressive Disorder

MFFT	=	Matching Familiar Figures Test
MG2+	=	Magnesium 2+
MRI	=	Magnetic Resonance Imaging
MRS	=	Magnetic resonance spectroscopy
MSRS	=	Manic State Rating Scale
NCBRF-TIQ	=	Nisonger Child Behavior Rating Form-Typical IQ Version
NF-kB	=	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NIH	=	National Institute of Health
NIMH	=	National Institute of Mental Health
NMDA	=	N-Methyl-D-Aspartate (receptor)
OAS	=	Overt Aggression Scale
Oxy	=	Oxymetholone
PARS	=	Pediatric Anxiety Rating Scale
SAICA	=	The Social Adjustment Inventory for Children and Adolescents
PANSS	=	Positive and Negative Syndrome Scale
PGBI-10M	=	Parent General Behavior Inventory-10 Item Mania Scale
PI3K	=	PhosphatidylInositol-3 Kinase
PIP2	=	PhosphatidylInositol-4,5,diPhosphate
PKA	=	Protein Kinase A
PKC	=	Protein Kinase C
PLC	=	Phospholipase C
PLB	=	placebo
PMT	=	Proteus Maze test
POMS	=	Profile of Mood States ratings
PP2A	=	Phosphates
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Raf	=	Rapidly Accelerated Fibrosarcoma/ serine/threonine-specific protein kinases
RBANS	=	Repeatable Battery for the Assessment of Neuropsychological Status
RT	=	Reaction Time task
RCTs	=	Randomized Controlled Trials
Risp	=	Risperidone
SGA	=	Second Generation Antipsychotics
SMD	=	Severe Mood Dysregulation
SR	=	Systematic Review
ST	=	Stroop Test
STRM	=	Short -term recognition Memory test
TBW	=	Total Body Weight
TESS	=	Treatment Emergent Symptom Scale
TSH	=	Thyroid Stimulating Hormone
VABS	=	Vineland Adaptive Behaviour Scale
Val	=	Divalproex Sodium
VAS	=	Visual Analogue Scale for behaviour
WISC-R	=	Wechsler Intelligence Scale for Children Revised
YMRS	=	Young Mania Rating Scale

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Gabriele Masi was in the advisory boards for Eli Lilly, Shire and Angelini, has received research grants from Eli Lilly, Shire, and Lundbeck, and has been speaker for FB, Eli Lilly, Shire, Lundbeck, and Otsuka. All the other authors do not have conflicts of interest to disclose.

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