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REVIEW

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Lithium use in childhood and adolescence, peripartum, and old age: an umbrella review

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Abstract

Background Lithium is one of the most consistently effective treatment for mood disorders. However, patients may show a high level of heterogeneity in treatment response across the lifespan. In particular, the benefits of lithium use may vary in special clinical conditions. The aim of this study was to test this hypothesis by conducting an umbrella review on the efficacy and safety of lithium in childhood and adolescence, peripartum and old age.

Methods We applied the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (PRISMA) to identify systematic reviews/meta-analyses on the efficacy and/or safety of lithium in mood disorders in special clinical conditions: (i) childhood and adolescence; (ii) peripartum (pregnancy, postpartum and lactation); (iii) old age. The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) tool was used to assess the risk of bias. Overlap in primary studies across systematic reviews was calculated through the Corrected Covered Area (CCA).

Results We included 20 independent studies, for a total of 8209 individuals treated with lithium. Regarding paediatric age, efficacy and safety results suggested that lithium may be superior to placebo in bipolar disorders (BD) and not associated with serious adverse events. Nevertheless, primary available data are very limited. Efficacy in paediatric major depressive disorder (MDD) is not clear. During peripartum, lithium use was superior to non-lithium in preventing mood episodes and it was associated with low risk of congenital anomalies and with normal child neurodevelopment. Regarding old age, limited evidence supported lithium as an effective treatment in BD and resistant MDD; low doses should be used in this population. Systematic reviews on paediatric age showed the lowest risk of bias (80% of the studies at low risk). The CCA range of included studies was 13–47%.

Conclusions This umbrella review supports the use of lithium across the lifespan, including special clinical condition. Nevertheless, more studies with increased methodological homogeneity are needed.

Keywords Lithium, Childhood, Adolescence, Paediatric, Peripartum, Postpartum, Pregnancy, Lactation, Elderly, Old age

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Introduction

Lithium is one of the most consistently effective drug treatment for mood disorders (Kessing et al. 2018; Geddes et al. 2004; Baldessarini et al. 2019). It has been approved for both adults and children and it is currently used from the age of 12 years until old age. However, clinical profiles of patients with mood disorders show a high level of heterogeneity during the course of life (Akiskal 1989; McIntyre et al. 2022). While this variety of clinical presentation has been adequately addressed in the literature (Torre-Luque et al. 2019; Sajatovic et al. 2022; Meter et al. 2011), lithium treatment response across the lifespan is less well-studied. Specifically, it remains unclear whether the benefits of lithium use may vary in special clinical conditions. In particular, paediatric age, peripartum, and old age, should be considered separately in the pharmacological management of mood disorders, as special clinical conditions deviating from the normal distribution of patient's characteristics. Many biological changes take place during these stages of life and may influence efficacy and safety of lithium use. During childhood and adolescence, the nervous system undergoes growth and development at a remarkable pace and may be differently influenced by lithium use. In parallel, earlier start of lithium treatment is associated with a better clinical outcome and increased probability of response to the drug (Vieta et al. 2018; Kessing et al. 2014). Similarly, the management of women with mood disorders during the peripartum period (including both pregnancy and the postpartum period, according to DSM-5) is associated with clinical concerns because of the inherent risks related to the disorders themselves as well as to their treatment (Tosato et al. 2017; Poels et al. 2018a; Yonkers et al. 2004). Regarding old age, the higher rates of physical and cognitive comorbidity in older adults, their alterations in social risk factors, and the greater likelihood of polypharmacy, all suggest that this population should be considered separately (Cooper et al. 2011). Furthermore, the age-related pharmacodynamic and pharmacokinetic changes may render older patients with mood disorders more susceptible to lithium's adverse events (Chan et al. 2020).

Although previous reviews separately considered the use of lithium in paediatric age (Duffy et al. 2018; Amerio et al. 2018), during the peripartum period (Wesseloo et al. 2017) and in geriatric populations (Cooper et al. 2011), no study to date has synthesised the evidence on lithium efficacy and safety in these three special clinical conditions. An umbrella review can therefore overcome this shortcoming and comprehensively evaluate the benefits of lithium use across lifespan. Accordingly, the aim of this study was to evaluate and fill-out the evidence of systematic reviews and meta-analyses focusing on the efficacy and/or safety of lithium use in mood disorders occurring in the above-mentioned special clinical condition. For each special condition, we assessed the risk of bias and the degree of overlap in studies of included systematic reviews.

Methods

Search

We applied the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses *(PRISMA)* criteria (http://www.prismastatement.org/) to identify systematic reviews and meta-analyses reporting results on the efficacy and/or safety of lithium use in mood disorders in special life stages: (i) childhood and adolescence (patients < 18 years old); (ii) peripartum, including data on pregnancy, postpartum and lactation; (iii) old age.

Studies were still eligible when their scope was not exclusively focused on lithium (i.e. systematic reviews on the pharmacological treatment of one of the included special clinical conditions) but if they focused on mood disorders and separately reported results on lithium (i.e. meta-analytic results on lithium, synthesis tables providing results on lithium). Studies were not excluded based on their risk of bias (assessed as described below), but potential biases were highlighted and discussed in the current review. Details of the search and article eligibility criteria can be found in the supplement. Eligibility was established with consensus obtained through Delphi rounds.

Data extraction

Specific data of the eligible full-version articles were carefully extracted and filled into the developed extraction form. The extracted outcomes, when available for each eligible study, consisted of the following: (i) number of original studies included in the systematic review; (ii) type of included studies; (iii) total number of patients treated with lithium; (iv) description of patients treated with lithium; (v) specific focus on lithium (Yes/No) (vi) primary and secondary outcomes; (vii) efficacy findings; (viii) safety findings; (ix) meta-analytic data (Yes/No), (x) conclusions.

Risk of bias

Included systematic reviews were assessed for their risk of bias through the Risk of Bias in Systematic Reviews (ROBIS) tool (Whiting et al. 2016). There are three phases in ROBIS, including assessing relevance, identifying concerns with the review process, and judging risk of bias. Phase one of ROBIS tool includes one item, which mainly evaluates whether the participants, exposures, comparators and outcomes match the target question. The answers are "yes," "no," "partial," and "uncertain".

Phase two includes four domains: (1) study eligibility criteria; (2) identification and selection of studies; (3) data collection and study appraisal; (4) synthesis and findings. The answers to phase two questions can be "yes," "probably yes," "probably no," "no" and "no information". The bias associated with each domain is judged as "low," "high," or "unclear" depending on the answers to each question. Phase three focuses on whether the systematic review in its entirety is at risk of bias. In this phase, the following questions are taken into account: (1) did the interpretation of findings address all the concerns identified in domains 1 to 4; (2) was the relevance of identified studies appropriately considered in review's research question; (3) did reviewers avoid emphasising results based on their statistical significance? Possible answers to these questions are the same as phase two. Based on the answers to the questions in phase three, the overall risk of bias in the systematic reviews were rated as "low," "high," or "unclear." Different investigators independently evaluated the risk of bias of all the included systematic reviews, and the disagreements were resolved through consensus.

Analysis of degree of overlap in studies

Overlap in umbrella-reviews indicates the degree to which the included reviews address the same or different primary research literature. Overlap in primary studies across systematic reviews was calculated through the Corrected Covered Area (CCA) (Hennessy and Johnson 2020). The current guidelines for generating the CCA involve first creating a citation matrix of all primary studies (rows) included for each review (columns), where primary studies, in specific reviews, are indicated with a check mark; duplicate rows (i.e., identical primary studies) are removed so that all the instances of that primary study appearing across reviews are noted in a single line. Next, calculate CCA (Pieper et al. 2014):

$$CCA = \frac{N - r}{(r \times c) - r}$$

where N is the total number of included publications (including double counting), in evidence synthesis (this is the sum of the ticked boxes in the citation matrix); r is the number of rows (number of index publications); and c is the number of columns (number of reviews). CCA is a proportion that can be represented as a percentage.

Results

At the end of the eligibility process, we included 20 independent trials, for a total of 8209 individuals treated with lithium. In particular, 5 systematic reviews were included in the paediatric age section for a total of 2661 individuals treated with lithium, 10 systematic reviews were included in the peripartum section for a total of 3872 individuals treated with lithium, and 5 systematic reviews were included in the old age section for a total of 1676 individuals treated with lithium.

All included studies were written in English, although this was not a prerequisite. Further information on the strategy and results of the search can be found in the Supplement. The results of our search are shown as a PRISMA flowchart in Additional file 1: Figure S1 with the reasons of exclusion.

Table 1 provides a description of the included studies, including information on study population, study design, efficacy, safety, conclusions, and limitations.

Children and adolescents

The five systematic reviews included in the children and adolescents section involved a total of 2661 individuals treated with lithium (Table 1). Among the reviews, three were specifically focused on lithium (Duffy et al. 2018; Amerio et al. 2018; Pisano et al. 2019) while the others reported results also on other pharmacological treatments for juvenile bipolar disorders (BD) (Liu et al. 2011; Yee et al. 2019). Most reviews included a small number of studies (< 10); the systematic review including the largest number of primary studies was Amerio et al. (2018), which reported data from 30 studies. One systematic review included only randomised, double blind controlled trials (Duffy et al. 2018), while the others also considered open label and observational studies (Amerio et al. 2018; Pisano et al. 2019; Liu et al. 2011; Yee et al. 2019). All reviews involved children and adolescents with BD; one meta-analysis specifically focused on children experiencing a manic or mixed episode with comorbid attention-deficit hyperactivity disorder (ADHD) (Duffy et al. 2018). Most included reviews reported data on both efficacy and safety, while Liu et al. (Amerio et al. 2018) provided results only on efficacy. All reviews highlighted that data available were very limited.

Efficacy

Only Duffy et al. (2018) provided meta-analytic findings. The findings specified that there was a lack of evidence to inform the question as to the effectiveness of lithium in paediatric BD of the classical type and that most studies included prepubertal children diagnosed with protracted manic/mixed episodes mostly with comorbid ADHD. In this context, efficacy results suggest that lithium may be superior to placebo (standardized mean difference [SMD] − 0.42, 95% confidence interval [CI] − 0.88 to 0.04), it is comparable to sodium divalproex (SMD − 0.07, 95% CI − 0.31 to 0.18), but significantly less effective than risperidone (SMD 0.85, 95% CI 0.54 to 1.15). The other included reviews reported that lithium was

Table 1 Characteristics of included studies

Study	Number of primary studies	Design of primary studies	Number of individuals treated with Li^+	Patients' description	Specifically focused on lithium	Specific outcomes on Li^+	Meta-analytic findings on Li^+ [a]	Findings on efficacy	Findings on safety	Conclusions
Liu et al. 2011	7	Open label, double-blind studies	151	Children (< 18 years) with BD	No	Efficacy of Li^+ for paediatric BD	No	Open-label: response rates: 23%-55%; Double-blind: 1/3 found Li^+ to induce long-term stabilisation	–	Limited data available
Amerio et al. 2018	30	RCTs, observational studies	1320	Children and adolescents (< 18 years) with BD treated with Li^+ monotherapy or combined with other drugs	Yes	Safety and efficacy of Li^+ for paediatric BD	No	Li^+ monotherapy: efficacy for acute mania in up to 50% of patients; some evidence of long-term maintenance efficacy Combination therapy: some evidence for Li^+ + APs and Li^+ + DVP	Li^+ generally safe in the short term. Most common AEs: gastrointestinal, polyuria or headache	Li^+ reasonably safe and effective in children and adolescents with BD in the short-term
Duffy et al. 2018	4	RCTs	176	Children and adolescents (< 18 years) with BD experiencing a manic or mixed episode	Yes	Efficacy and tolerability of Li^+ for paediatric mania	Yes	Li^+ > plc and comparable to DVP, but < Risp for treating manic/mixed episodes and comorbid ADHD	Li^+ not associated with serious AEs, and generally well tolerated with common AEs similar to those reported in adults	Limited data to suggest that Li^+ is effective and tolerable for some forms of paediatric mania

Table 1 (continued)

Study	Number of primary studies	Design of primary studies	Number of individuals treated with Li^+	Patients' description	Specifically focused on lithium	Specific outcomes on Li^+	Meta-analytic findings on Li^+ [a]	Findings on efficacy	Findings on safety	Conclusions
Pisano et al. 2019	19	Open label, RCTs	871	Children and adolescents with BD and MDD	Yes	Efficacy and safety of Li^+ for paediatric BD and MDD	No	Li + effective for manic symptoms, both in the acute phase and as maintenance strategy. Efficacy on depressive symptoms less clear	Generally, Li + resulted relatively safe	Li + is effective and well-tolerated in paediatric BD. Further evidences are needed for other clinical indications
Yee et al. 2019	5	RCTs, open-label	143	Youths (< 18 years) with BD treated for at least 6 months	No	Efficacy and safety of Li^+ for the maintenance of juvenile BD lasting ≥ 24 weeks	Yes	Clinical response rate: 51.1% [CI = 18.1 to 29.7]	Mean AE risk: 23.9% [CI = 0 to 164]	Li^+ may reduce long-term morbidity in juvenile BD. Limited data
Peripartum and lactation										
Doucet et al. 2011	10	Open, retrospective, prospective, studies, case reports	73	Women with PP mood episodes with psychotic features exposed to Li^+	No	Effectiveness of Li^+ for the prevention or treatment of PP psychosis	No	5 studies supported the prophylactic effect of Li^+, 3 studies supported the use of lithium in treating PP	–	Preliminary evidence suggests Li^+ to be effective for PP psychosis prevention and treatment
Galbally et al. 2010	12	Case–control, prospective studies, case series	773	Women exposed to Li^+ during pregnancy	No	Pregnancy AEs and child developmental outcomes (safety)	No	–	Ebstein's anomaly, prematurity and ↑ birth weight reported. Negative results in cohort-controlled studies	Limited data available

Table 1 (continued)

Study	Number of primary studies	Design of primary studies	Number of individuals treated with Li^+	Patients' description	Specifically focused on lithium	Specific outcomes on Li^+	Meta-analytic findings on Li^+[a]	Findings on efficacy	Findings on safety	Conclusions
Uguz et al. 2016	5	Case series, case reports	26	Women with BD treated with Li^+ during lactation	No	Infant AEs (safety)	No	–	Few clinically significant AEs reported	The incidence of AEs in infants exposed to Li^+ is very low
Pacchiarotti et al. 2016	6	Case series, case reports	35	Women with BD treated with Li^+ during lactation	No	Infant AEs (safety)	No	–	No clinically significant AEs reported	Available data supports the use of Li^+ as during breastfeeding
Haskey et al. 2017	2	Retrospective cohort studies	18	Women exposed to Li^+ during pregnancy	No	Child developmental outcomes (safety)	No	–	No AEs on cognitive development	Data on Li^+ exposure are reassuring but are both limited and low quality
Poels et al. 2018	9	Cohort studies, case reports	107	Women exposed to Li^+ during pregnancy	Yes	Neurodevelopmental consequences for the child (safety)	No	–	Clinical cohort studies: Li^+ associated with normal development. Case reports: Most (4/5) reported at least one AE	Interpretation is difficult due to study heterogeneity
Imaz et al. 2019	13	Case reports, case series	39	Women treated with Li^+ during lactation	Yes	AEs or developmental outcomes in infants (safety)	No	–	80% of breasted infants showed no AE 20.% showed at least one AE	Heterogeneity and low-moderate quality of studies
Newmark et al. 2019	12	Case reports	37	Women treated with Li^+ during lactation	Yes	Infant AEs (safety)	No	–	AEs were reported in 9.4% of breastfed infants	Limited data

Table 1 (continued)

Study	Number of primary studies	Design of primary studies	Number of individuals treated with Li^+	Patients' description	Specifically focused on lithium	Specific outcomes on Li^+	Meta-analytic findings on Li^+ [a]	Findings on efficacy	Findings on safety	Conclusions
Fornaro et al. 2020	29, 13 for meta-analysis	Case–control, cohort, and interventional	2,622	Women with BD treated with Li^+ during pregnancy and the PP compared to unexposed control subjects (both women in the general population and patients with affective disorders not exposed to Li^+)	Yes	Relapse prevention (efficacy); risk of any malformation (safety)	Yes	Li^+ > no Li^+ in relapse prevention (OR = 0.16, 95%CI = 0.03–0.89)	Li^+ associated with ↑ risk of any congenital anomaly (OR = 1.81, 95%CI = 1.35 to 2.4); cardiac anomalies (OR = 1.86, 95% CI = 1.16 to 2.96); spontaneous abortion (OR = 3.77, 95% CI = 1.15 to 12.39). Compared only with unexposed mood disorder patients, significant results only for spontaneous abortion and cardiac anomalies (in 1st trimester). No association with preterm birth and low birth weight	Li^+ exposure-associated risk at any time during pregnancy is low; ↑ risk for 1st-trimester or higher-dosage exposure
Uguz 2020	9	Any design, including case reports and case series	142	Women with BD exposed to Li^+ during pregnancy and the PP	No	Relapse prevention (efficacy)	No	BD recurrence rates: Pregnancy: 22.7% PP: 20.3%	–	Li^+ effective in preventing new mood episodes in BD during the perinatal period
Advanced age										
Ross 2008	3	Prospective, RCTs	38 using Li^+ followed by discontinuation	Patients > 65 years with MDD treated with Li^+ augmentation to AD, followed by Li^+ discontinuation	Yes	Relapse prevention (efficacy)	No	Recurrence rates after discontinuation: 50% relapse over ~6 months follow-up	–	Risk of relapse in elderly patients whose Li^+ augmentation treatment for MDD is discontinued. Limited data
Cooper et al. 2011	5	Open-label, RCTs	64	Patients > 55 years with treatment resistant MDD treated with Li^+ augmentation	No	Response to treatment (efficacy)	Yes	The overall response rate for Li^+ augmentation was 42% (95% CI = 21–65)	–	Replicated evidence for Li^+ augmentation as effective in treatment resistant MDD

Table 1 (continued)

Study	Number of primary studies	Design of primary studies	Number of individuals treated with Li^+	Patients' description	Specifically focused on lithium	Specific outcomes on Li^+	Meta-analytic findings on Li^+ [a]	Findings on efficacy	Findings on safety	Conclusions
Rej et al. 2012	10	RCTs, case–control studies, retrospective, cross-sectional, descriptive	835	Patients > 65 years using Li^+	Yes	Renal AEs (safety)	No	–	ARF incidence: 1.5% per person-year, CRF prevalence: 1.2% to 34%; The prevalence of NDI:1.8% to 85%	No evidence to suggest that Li^+ should be avoided in elderly patients
De Fazio et (2017)	15	Retrospective, prospective, RCTs	701	Patients > 50 years with BD	Yes	Efficacy and safety of Li^+ in the treatment and prevention of the mania	No	In the 2 RCTs: Li^+ > plc and ≥ other mood stabilizers; Recent retrospective/prospective studies: average 72% positive response to Li^+	Less AEs at lower doses	Evidence suggests that Li^+ is effective and well tolerated; limited evidence
Sun et al. 2018	37	Case reports	38	Patients > 65 years using Li^+ with BD or MDD	Yes	Li^+ toxicity in elderly (safety)	No	–	Most common AEs: neurotoxicity, renal and cardiovascular toxicity. Precipitating factors: polypharmacy, comorbidity, high Li^+ concentration	Lower doses of Li^+ should be used in the elderly

[a] Meta-analytic data were considered only if separately reporting results on lithium

↑ increase(d), > superior, < inferior, ≥ superior or comparable, ∼ about, *AD* antidepressants, *ADHD* Attention-deficit hyperactivity disorder, *AE(s)* adverse event(s), *AP(s)* antipsychotic(s), *ARF* acute renal failure, *BD* Bipolar Disorder, *CRF* Chronic renal failure, *DVP* sodium divalproex, *CI* confidence interval, *Li*$^+$ lithium, *MDD* major depressive disorder, *NDI* nephrogenic diabetes insipidus, *OR* odds ratio, *plc* placebo, *PP* postpartum, *RCT* randomised-control trial, *Risp* Risperidone, *SMD* standardised mean difference