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Review/Meta-analyses

Safety and efficacy of lithium in children and adolescents: A systematic review in bipolar illness

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ABSTRACT

Introduction: Many clinicians are reluctant to use traditional mood-stabilizing agents, especially lithium, in children and adolescents. This review examined the evidence for lithium's safety and efficacy in this population.
Methods: A systematic review was conducted on the use of lithium in children and adolescents with bipolar disorder (BD). Relevant papers published through June 30th 2018 were identified searching the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Library.
Results: 30 articles met inclusion criteria, including 12 randomized controlled trials (RCTs). Findings from RCTs demonstrate efficacy for acute mania in up to 50% of patients, and evidence of long-term maintenance efficacy. Lithium was generally safe, at least in the short term, with most common side effects being gastrointestinal, polyuria, or headache. Only a minority of patients experienced hypothyroidism. No cases of acute kidney injury or chronic kidney disease were reported.
Conclusions: Though the available literature is mostly short-term, there is evidence that lithium monotherapy is reasonably safe and effective in children and adolescents, specifically for acute mania and for prevention of mood episodes.

1. Introduction

The diagnosis of bipolar disorder (BD) in children and adolescents has been a controversial topic [1], with much concern about risks of treating it [2], with concerns about the harms of antipsychotic agents in particular [3]. An alternative to antipsychotic agents would be mood-stabilizing drugs like lithium, yet clinicians also are reluctant to use that agent, especially with apprehension regarding cognitive side effects [4], as well as about long-term medical risks, such as hypothyroidism and chronic renal insufficiency [5]. Further, many clinicians seem to be sceptical about the efficacy of lithium in children.

This paper seeks to shed light on these concerns, with the first systematic review on the safety and efficacy of lithium in children and adolescents with BD.

2. Materials and methods

As done before [6,7], this review was conducted according to methods recommended by the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8,9].

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2.1. Information sources and search strategy

Studies were identified searching the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Library. We combined the search strategy of free text terms and exploded MESH headings for the topic of treatment with lithium in children and adolescents combined as following: ((((((Lithium) OR Lithium carbonate) OR Lithium carbonate[MeSH Terms])) AND (((Children) OR Adolescent) OR Adolescent[MeSH Terms])) AND (((((((Bipolar disorder) OR BD) OR Bipolar) OR Manic depressive disorder) OR Manic depressive) OR Manic) OR Bipolar disorder[MeSH Terms])) AND ((((treatment*) OR therap*) OR pharmacotherap*) OR Therapeutics[MeSH Terms]). The strategy was first developed in MEDLINE and then adapted for use in the other databases (Appendix A in Supplementary material). Studies published in English through June 30th 2018 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field.

2.2. Inclusion criteria

2.2.1. Study population and study design

We considered studies that included children and adolescents with BD treated with lithium both in monotherapy and in combination with others psychotropic drugs. BD was considered if diagnostic criteria used were specified. Studies conducted on youths with different disorders than BD (e.g. dysphoric mood dysregulation disorder) were excluded (i.e. [10–12]:). Participants of both sexes younger than 18 years of age were considered. Studies conducted on subjects with physical comorbidities such as epilepsy were excluded as non-representative of the study population [13].

Among hospital-based studies, inpatients, day-hospital and outpatient subjects were included, while emergency care records were excluded as non-representative. All experimental and observational study designs were included apart from case reports and case series. Narrative and systematic reviews, letters to the editor, and book chapters were excluded.

2.2.2. Outcomes

The primary outcome was lithium effectiveness in children and adolescents with BD. Secondary outcomes were i) starting dose and dosing strategy, ii) brain-to-serum lithium association, and iii) safety and tolerability of lithium.

2.2.3. Study selection and data extraction

Identified studies were independently reviewed for eligibility by two authors (AA, FS) in a two-step process: A first screening was performed based on title and abstract, and then full texts were retrieved for a second screening. At both stages disagreements by reviewers were resolved by consensus. Data were extracted by two authors (AA, FS) and supervised by a third author (SNG) using an *ad-hoc* developed data extraction spreadsheet. The data extraction spreadsheet was piloted on 10 randomly selected papers and modified accordingly.

3. Results

Two hundred and twelve potential studies were identified from the selected databases and after cross-checking references of relevant articles. After removing duplicates, 152 articles were retrieved. Studies were screened and selected on the basis of pre-specified inclusion and exclusion criteria (Fig. 1). The search identified 30 articles that were included in the systematic review.

3.1. Included studies

The characteristics of included studies are reported in Table 1. Twelve (40%) of the 30 studies were randomized controlled trials (RCTs) of which only one was longer than 6 months in duration. Most studies (n = 19, 63%) were short-term (8 weeks or less), while 4 studies (13%) provided long-term data of 6 months or longer. The smallest study included 6 subjects while the largest considered a sample of 279 subjects. The majority of the studies were conducted in North America (N = 28, 93%). In all the considered studies, diagnosis were based on the Diagnostic and Statistical Manual (DSM) criteria and were established using validated assessment scales (Table 1).

3.2. Outcomes

Selected studies included children and adolescents with BD treated with lithium. Both lithium monotherapy and lithium in combination with adjunctive agents were included. Data about starting dose and dosing strategy, brain-to-serum lithium association, safety and tolerability were also reported (Table 2).

4. Bipolar illness

Thirty studies assessed the use of lithium in children and adolescents with BD (Table 2). The majority of the selected studies (N = 22/30, 73%) were conducted on BD patients treated with lithium monotherapy. Eleven studies (37%) were specific for BD-I patients.

4.1. Lithium monotherapy

4.1.1. Manic or mixed episodes

Three RCTs reported improvements in manic or mixed symptoms and overall functioning in manic BD children and adolescents with lithium treatment [14,20,21]. Over 50% of patients met response and remission criteria in one out of three of the cited studies [14]. These results were supported by three prospective non-randomized cohort studies [18,22,23] and one retrospective cohort study [24]. No significant difference in exacerbation rates between subjects treated with lithium and those switched to placebo was detected in only one RCT with a very short stabilization period (two weeks) [25].

Considering bipolar subgroups, lithium effectiveness for manic symptoms was greater in adolescent-onset compared to prepubertal-onset patients in one study [23]. Manic adolescents with comorbid attention deficit hyperactivity disorder (ADHD) showed less robust and slower improvement with lithium compared to non-comorbid patients, both in a randomized and in a non-randomized trial [26,27]. In patients with substance abuse and BD, lithium was an effective for both conditions in one RCT [15].

4.1.2. Depressive episodes

A 6-week prospective non-randomized cohort study in BD-I depressed children and adolescents treated with lithium reported response and remission rates of 48% and 30%, respectively, with a large reduction in Children's Depression Rating Scale-Revised (CDRS-R) scores (standardized effect size Cohen's d = 1.7) [28].

4.1.3. Prophylaxis

Three prospective non-randomized cohort studies reported long-term positive response to lithium treatment [29,30], especially in those who responded to acute treatment with lithium [31].

In a 18-month prospective non-randomized cohort study, 35% (N = 13/37) of patients who discontinued prophylactic lithium therapy showed nearly three times higher relapse rates compared