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REVIEW ARTICLE

Lithium in bipolar depression: A review of the evidence

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Abstract

Background: Lithium is widely used as treatment of acute mania and as prophylactic therapy for bipolar disorder. International and national guidelines also consider lithium as a possible treatment of acute bipolar depression. Research on the use of lithium in bipolar depression, however, seems to be limited compared to the data available for its efficacy in the other phases of bipolar disorder.

Objective: To provide a systematic review of the evidence for lithium in the treatment of acute bipolar depression and provide directions for further research.

Method: A systematic review of clinical studies investigating the use of lithium in bipolar depression was performed using preferred reporting items for systematic reviews and meta-analyses guidelines in Pubmed, Embase and Psychinfo using the medical subjects headings and free text terms "lithium," "bipolar depression," "dosage," "serum concentration" and "bipolar disorders."

Results: This review included 15 studies with a total of 1222 patients, between the age of 18 and 65, suffering from bipolar depression of which 464 were treated with lithium. There are currently only limited and low-quality data on the efficacy of lithium as a treatment of bipolar depression. It appears that there have been no placebo controlled randomized controlled trials with lithium concentrations that are considered to be therapeutic. The older studies suffered from limitations such as small sample sizes, insufficient treatment lengths, and insufficient monitoring of serum concentrations.

Conclusion: In contrast to data for the treatment of mania and prophylaxis, robust data on the efficacy of lithium in bipolar depression is currently lacking, making it impossible to make conclusions regarding efficacy or inefficacy, for which further research is needed.

KEYWORDS
bipolar depression, bipolar disorder, lithium

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1 | INTRODUCTION

Approximately 1% of the world population suffers from bipolar disorder, a condition characterized by recurrent and alternating periods of (hypo-)mania and depression. Depressive episodes in bipolar disorder typically do not respond well to the standard treatments for unipolar depression and patients report an overall lower quality of life than the general population and are known to have a significantly lower life expectancy (ten Have et al., 2002; Yatham et al., 2018). Depressive episodes comprise by far the largest part of non-euthymic mood states in bipolar patients of both type I and II. Even when correctly diagnosed and treated, patients with bipolar disorder spend up to 36% of their lifetime after disease onset suffering from depressive symptoms (Kupka et al., 2007).

Lithium is considered a cornerstone of the treatment of bipolar disorder ever since its registration by the Food and Drug Administration in 1971. The exact mechanism of its effect remains unclear, but lithium is hypothesized to have a stabilizing effect on circadian genes and neurotransmission and to enhance the "stress resistance" of the brain. The protective effect against mood episodes is partly elicited by diminishing the excitability of neurons by stabilization of the intracellular electrolyte balance and sodium pumps. Furthermore, lithium intervenes in second messenger systems as well as in monoaminergic pathways, and restores the diminished activity of the CAMP-Response Element Binding Protein through mitochondrial processes (Alda, 2015).

The efficacy and effectiveness of lithium has been robustly proven for treatment of manic episodes and prophylaxis of recurrent episodes (Malhi et al., 2017; McKnight et al., 2019; Yatham et al., 2018). Several guidelines also consider lithium to possess anti-suicidal effects (Yatham et al., 2018). The optimal serum concentrations for prophylaxis and treating acute mania have been well established through multiple studies. In contrast, data on the use in bipolar depression seems rather limited. One older meta-analysis of pharmacological interventions in bipolar disorder states that there were no robust data available to assess the effectiveness of lithium in treating bipolar depression (Selle et al., 2014). Two recent systematic reviews and meta-analysis reached the same conclusion (Fountoulakis et al., 2022; Rakofsky et al., 2022). At the same time, several guidelines like those from the "Canadian Network for Mood and Anxiety Treatments" (CANMAT) and the "International Society for Bipolar Disorders" (ISBD) (Yatham et al., 2018) advise treatment of bipolar depression with lithium and recommend a target serum concentration of 0.8–1.2 mmol/L.

Given the cost-effectiveness of lithium and its already widespread use in bipolar disorder, a more in-depth evaluation of the studies on lithium in bipolar disorder is warranted, in particular to formulate recommendations for further research on the effectiveness of lithium in bipolar depression.

2 | METHOD

All procedures were performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The selection was conducted in two stages: an initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant papers, followed by screening the full papers assessed for eligibility. Two authors reached consensus on the inclusions of studies.

We performed a literature search in Pubmed, Embase and Psychinfo using medical subjects headings terms and free text searches for the terms: "lithium," "bipolar depression," "dosage," "serum concentration" and "bipolar disorders." Original articles were included if they described the usage of lithium in the treatment of bipolar depression in adult patients, if there was a description of the dosage used or lithium serum concentration, and when published in English. Case reports were excluded (Figure 1).

The results of the studies were interpreted according to the following definitions of response and remission (Riedel et al., 2010). 'Response' was defined as a reduction of symptoms of 50% or more on the depression scale used in the study. 'Remission' was defined as a complete remission of clinical symptoms or a score lower than the cut-off value for remission of the depression scale that was used. If the results of the study could not be interpreted according to these definitions, but the researchers describe a positive clinical effect, it was classified as "clinical improvement." We did not apply the ISBD definitions specifically laid out for bipolar depression (Tohen et al., 2009), due to a lack of sufficient detail provided in most which precluded their application.

3 | RESULTS

In this systematic review, 15 studies with a total of 1222 patients suffering from bipolar depression were included (see Table 1). Four hundred and sixty four patients were treated with lithium, the remaining patients were part of a control or placebo group. Three randomized controlled trials (RCTs) investigated lithium in bipolar depression. Twelve non randomized longitudinal studies were performed, of which six studies were of a cross-over design with placebo. Two further studies investigated lithium after a placebo washout and three studies assessed lithium as add-on. One longitudinal study was of a purely observational design. The studies will be discussed according to study design and level of evidence.

3.1 | Randomized controlled trials

Three RCTs were performed, comparing lithium to quetiapine and placebo in a double-blind design (lithium $n = 136$, placebo $n = 133$) (Young et al., 2010), to lamotrigine in a single blinded design (lithium

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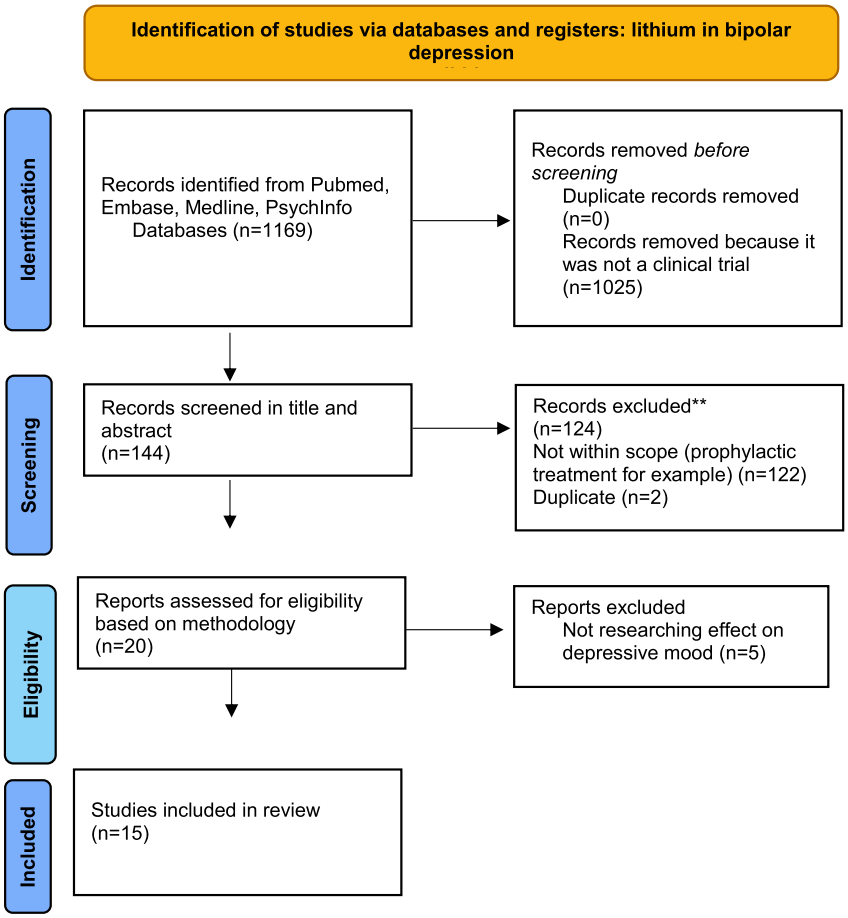

FIGURE 1 Flowchart of the process of study inclusion.

$n = 54$, lamotrigine $n = 44$) (Suppes et al., 2008), and to venlafaxine in an unblinded design (lithium $n = 40$, venlafaxine $n = 43$) (Amsterdam & Shults, 2008) (see Table 1). Only the first mentioned RCT included patients with bipolar type I. The interventions lasted between 8 and 16 weeks and validated questionnaires were used to assess outcomes. Quetiapine was found to be superior to lithium at serum concentrations of 0.61 mmol/L, and placebo and lithium scored comparatively (Young et al., 2010). In the single blinded comparison to lamotrigine, lithium was not superior at a median serum concentration of 0.8 mmol/L (Suppes et al., 2008). There was a significant drop-out rate in both treatment arms. In the unblinded comparison to venlafaxine, mean lithium concentrations of 0.64 mmol/L were achieved. Venlafaxine was more effective in this comparison and the drop-out rate for the lithium treatment arm was 62.5%. An exclusion criterium for all three studies was previous non-response to either treatment. Furthermore, drop-out rates were high and all three research groups describe that lithium serum concentrations were generally lower than initially targeted.

3.2 | Cross-over studies

Six cross-over studies were undertaken using lithium and placebo, of which five were double-blinded (Baron et al., 1975; Goodwin et al., 1969, 1972; Mendels, 1976; Stokes et al., 1971) and one was single blinded (Noyes et al., 1974) (see Table 1). These studies mostly alternated treatment with lithium and placebo, employing treatment lengths of between two and 22 days, regardless of effect. One study only crossed over to placebo in case there was clinical response to lithium. Three studies used non-validated clinical observation scales (Goodwin et al., 1969, 1972; Stokes et al., 1971), the other three used validated depression scales. The number of patients per study varied between 9 and 40. All studies aimed for serum concentrations >0.8 mmol/L and—as far as is mentioned in the publications, these concentrations were achieved. Remission rates were between 38% and 83% and relapse rates under placebo were generally high 50%–66%. Only one study did not find a clinical difference between placebo and lithium (Stokes et al., 1971).

3.3 | Longitudinal designs without cross-over

Two studies studied lithium monotherapy during 28 days at serum concentrations of 0.88–1.37 mmol/L after a wash-out with placebo. One study was double-blinded (Donnelly et al., 1978), the other unblinded (Mendels & Frazer, 1973). The study groups consisted of 33 and 10 patients respectively. Response was found in 80% of patients in the study that rated response according to the guidelines, 64% of patients showed response in the study that used nurse observations and unvalidated questionnaires.

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TABLE 1 Studies investigating the effect of lithium in acute bipolar depression.

Author, year	Study design	Study population	Intervention, duration	Lithium dosage (mg/day)	Lithium serum concentration (mmol/L) mean/target concentration[a]	Primary outcome	Results in patients with bipolar depression
Randomized controlled trials (RCTs)							
Young et al. (2010)	Double-blind randomized placebo controlled trial	802 patients with bipolar type I or II according to the DSM IV, 136 patients in lithium arm	Lithium or quetiapine (300 and 600 mg) or placebo during 8 weeks	600–1800	0.61/0.6–1.2	MADRS	Lithium was not superior to placebo at a mean serum concentration of 0.61 mmol/L
Suppes et al. (2008)	Single blinded randomized trial without placebo control	102 patients with type II bipolar depression according to DSM IV, 54 patients received lithium. Exclusion if patients were non-responders to either drug in previously	Comparison to lamotrigine (200 mg) during 16 weeks	Minimum of 900, titrated using serum concentration	Median 0.8/0.8–1.2	HDRS two times per week	No difference between lithium and lamotrigine. Lithium remission $n = 27$, 55.1%. Substantial drop-out: 40 out of 102 patients did not drop-out (19 lithium, 21 lamotrigine)
Amsterdam and Shults (2008)	Unblinded, randomized trial without placebo control	83 patient with bipolar disorder type II according to DSMIV. 49 patients finished the study Exclusion if patients were non-responders to either drug in previously	Lithium compared to venlafaxine during 12 weeks	900, titrated using serum concentration	0.64/0.5–1.5	HDRS	Venlafaxine more effective than lithium. Remission lithium $n = 1$, 7.5%, response $n = 3$, 20%. Substantial drop-out in lithium group (25 out of 40)
Cross-over studies							
Stokes et al. (1971)	Double-bind cross-over design	38 episodes of bipolar depression were treated in 18 unique patients, 21 with placebo and 17 with lithium	Alternating treatment of lithium and placebo every 7–10 days	Unknown	0.93/<1.5	7-point clinical observation scale	No significant difference between lithium and placebo. Criteria of response and remission are not according to current definition

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TABLE 1 (Continued)

Author, year	Study design	Study population	Intervention, duration	Lithium dosage (mg/day)	Lithium serum concentration (mmol/L) mean/target concentration[a]	Primary outcome	Results in patients with bipolar depression
Baron et al. (1975)	Double-blind cross-over design	9 patients with bipolar depression out of 18 patients with depression	19 days of treatment with lithium, if there was clinical response, cross-over to placebo	Unknown	0.87/0.8–1.0	BHGS	Clinical improvement in *n* = 8, 88%. Relapse after placebo substitution 50%. Remission during placebo period *n* = 1 was excluded. Criteria of response are not in accordance to current guidelines
Mendels (1976)	Double-blind cross-over to placebo	13 patients with bipolar depression in a group of 21 patients with depression	Treatment with lithium up till 1.5 mmol/L during 21 days, cross-over to placebo for 7–22 days	Unknown	Unknown/1.5 or clinical improvement	Return to normal functioning next to HDRS, Beck depression inventory and BHGS	Remission *n* = 9, 69%, relapse *n* = 6, 66% during placebo substitution
Goodwin et al. (1969)	Double-blind cross-over to placebo	13 patients with bipolar depression out of 18 patients with depression	Alternating periods of 2–14 days of lithium and placebo. Total observation period 75 days	900–1300, based on body weight	Unknown/0.8–1.3	15-point observation scale	Remission *n* = 5, 38%; response criteria not in accordance to current guidelines better response to lithium in bipolar patients than in unipolar patients
Goodwin et al. (1972)	Double-blind cross-over to placebo	40 bipolar patients in a group of 52 patients with depression	Alternating periods of lithium and placebo. Lithium periods has a minimal length of 2 weeks, placebo of 6 days	Tablets of 300 mg, unknown amount	Unknown/unknown	15-point observation scale	Remission *n* = 12, 30%; response criteria not in accordance to current guidelines
Noyes et al. (1974)	Single blind cross-over to placebo	6 bipolar patients in a group of 22 patients with depression	Lithium during 2 weeks alternated by placebo periods of varying lengths	26 per kg	1.15/unknown	HDRS twice a week and nurse observation scale	Remission *n* = 5, 83%; response *n* = 1, 17% relapse during placebo substitution 67%

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TABLE 1 (Continued)

Author, year	Study design	Study population	Intervention, duration	Lithium dosage (mg/day)	Lithium serum concentration (mmol/L) mean/ target concentration[a]	Primary outcome	Results in patients with bipolar depression
Longitudinal designs without cross-over							
Donnelly et al. (1978)	Double-blind	33 patients with bipolar depression type I or II out of 53 patients with depression	Lithium during 28 days after placebo wash out of 5 days	Median 1500	0.9–1.3/unknown	Nurse observation and unvalidated questionnaire	Clinical improvement $n = 21$, 64%. Response criteria are not in accordance to current guidelines
Mendels and Frazer (1973)	Unblinded	10 bipolar patients out of 13 depressed patients	Lithium monotherapy during 28 days after initial wash-out	1200–2589	0.88–1.37/unknown	HDRS, depression inventory and clinical observation by nurses	Response $n = 8$, 80%
Kramlinger and Post (1989)	Double-blind, add-on	13 patients with bipolar depression according to DSM III	Lithium as add-on therapy to carbamazepine during 21 days	Average of 1116	0.8/unknown	BHGS	Clinical improvement $n = 6$, 46%, no remissions and response was not according to guidelines
Nelson and Mazure (1986)	Partial blinding of observers, add-on	9 patients with bipolar depression and psychotic symptoms according to DSM III	Lithium as add-on therapy to treatment with antidepressants or antipsychotics for a minimum of 2 weeks	600–1200	0.79/unknown	Clinical global improvement scale (CGI) consensus was reached between blinded and unblinded observer	Response $n = 8$, 89%
Price et al. (1986)	Unblinded, add-on	11 patients with bipolar depression according to DSM III	Lithium add-on therapy to antidepressant for 10 days if antidepressant monotherapy was ineffective	900–1500	Unknown/0.5–1.3	Short Clinical Rating scale (SCRS), HDRS	Response $n = 1$, 9%
Adler et al. (2011) (conference abstract)	Unblinded, observational	60 patients with type I bipolar disorder	6 weeks of treatment with lithium	unknown	0.4–1.1/n.a.	MADRS and HDRS	Decrease on both scales at serum concentrations 0.4–0.9 mmol/L with a maximum significance at 0.6 mmol/L

Abbreviations: BHGS, Bunney-Hamburg global scale; HDRS, Hamilton depression rating scale; MADRS, Montgomery and Åsberg Depression Rating Scale.

[a]In case mean lithium concentrations were unknown, the range is noted.

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Three other studies added lithium to existing treatment with carbamazepine, antidepressants or antipsychotics in add-on studies. One study was double-blinded (Kramlinger & Post, 1989), one partially blinded to observers (Nelson & Mazure, 1986) and one unblinded (Price et al., 1986). The number of treated patients was small: between 9 and 13 patients per study. No cases of remission were reported in the studies after treatment during 10–21 days. Two studies found clinically relevant response or improvement in 89% at a mean lithium serum concentration of 0.79 mmol/L (Nelson & Mazure, 1986) and 46% at 0.8 mmol/L (Kramlinger & Post, 1989). The one study of which achieved lithium serum concentrations were unknown, found response in 9% (Price et al., 1986). The exact concomitant medication was unknown for all three studies as was comorbidity.

One unblinded, purely observational study followed 60 patients with type I bipolar disorder and found the most significant decrease of MADRS and Hamilton depression rating scale when patients had serum concentrations of 0.4–0.9 mmol/L (Adler et al., 2011).

4 | DISCUSSION

In our systematic literature review of the effectiveness of lithium in bipolar depression we included 15 studies of varying quality (see Table 1). There were only three RCTs available, these found that lithium was not superior to placebo, quetiapine, lamotrigine or venlafaxine. There are, however, important limitations to these RCTs to consider. The achieved mean lithium serum concentration in the three RCTs was relatively low (0.61, 0.64 mmol/L and respectively median 0.8 mmol/L). It is important to note that in the study with the highest methodological quality (a large double-blind, randomized placebo-controlled trial; Young et al., 2010) only 61% of patients reached a lithium serum concentration within the target range of 0.6–1.2 mmol/L and a mean serum concentration of only 0.61 mmol/L was reached. In the second RCT (Amsterdam & Shults, 2008) in which there was no blinding and no placebo control group, the mean lithium serum concentration was also only 0.64 mmol/L. In the third RCT (Suppes et al., 2008) in which an antidepressant effect equal to that of lamotrigine was found, lithium concentrations were higher than the other two RCTs (median of 0.8 mmol/L, range 0.6–1.2 mmol/L), but the study design did not involve double blinding or a placebo comparison. Importantly, the effectiveness of lithium was never investigated in a double-blind and placebo-controlled trial with serum concentrations above 0.61 mmol/L. Finally, only patients with bipolar type II were included in the two smaller RCTs (Amsterdam & Shults, 2008; Suppes et al., 2008).

Opposed to the RCTs, the other 12 studies specifically targeted higher serum concentrations of lithium, and exhibited more effectiveness of its therapeutic effects. These studies, however, have significant limitations as well such as: small sample sizes, different lengths of treatment and observation, and often unknown serum concentrations. Furthermore, lithium dosages were often not adjusted to age, sex or weight in these earlier studies and the duration of treatment was often insufficiently long according to current standards, potentially leading to an underestimation of its effect. Also, concomitant usage of other psychopharmaceutical was often unclear in the add-on studies. Finally, in many studies the scale that was used to measure effect was not validated. Considering all studies, those with higher lithium serum concentrations demonstrated more favorable outcomes, but were also subject to considerable limitations. On the other hand, studies with stronger methodologies failed to achieve serum concentrations as advised in guidelines for treating depressive episodes in bipolar disorder. A limitation of the current review is that it was performed right before the publication of the new PRISMA guidelines, and thus, it relied on the previous version of the guidelines.

There are several possible explanations why so few good methodological studies on the effectiveness of lithium in bipolar depression are available. One may be the fact that until the introduction of the DSM III in 1980, bipolar depression was not considered as a separate entity. Hence, studies before the introduction of the DSM-III might have included patients suffering from bipolar depression or unipolar depression. The introduction of new compounds by the pharmaceutical industry might have stagnated further research into lithium, which was at the time already well established as a treatment for manic episodes and as prophylactic treatment. These new pharmaceutical compounds for bipolar disorder compromise antipsychotics such as quetiapine and lurasidon, mood stabilizers such as lamotrigine, and the introduction of combination therapies such as fluoxetine with olanzapine. These often gained on lithium in routine daily practice, possibly because they do not require regular monitoring of serum concentrations and were thought to have a better safety profile. Also, much attention was given to the many double-blind studies, usually initiated by pharmaceutical companies, that focused on these new pharmaceutical options. These newer drugs have now taken a prominent place in the treatment of bipolar disorders (Yatham et al., 2018).

5 | CONCLUSIONS

Based on the current systematic review, we conclude that the possible efficacy and effectiveness of lithium in the treatment of bipolar depression has not been thoroughly investigated. Given the widespread use and cost-effectiveness in other phases of bipolar disorder, we believe there is a need for exploring currently available "real world" clinical data, but in particular for large placebo-controlled randomized trials of adequate duration and investigating higher target serum concentrations, while using the specific ISBD definitions of response and remission in bipolar depression.

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None.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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