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Journal Title: Journal of Psychopharmacology

Article Number: 822161

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Lithium treatment for unipolar major depressive disorder: Systematic review

Juan Undurraga[1–3], Kang Sim[1,4], Leonardo Tondo[1,5,6], Ariel Gorodischer[7], Emilio Azua[8], Kai H Tay[4], David Tan[4] and Ross J Baldessarini[1,5] [GQ: 1]

Journal of Psychopharmacology
1–9

DOI: 10.1177/0269881118822161
journals.sagepub.com/home/jop

Abstract

Background: The potential value of lithium treatment in particular aspects of unipolar major depressive disorder remains uncertain.
Methods: With reports of controlled trials identified by systematic searching of Medline, Cochrane Library, and PsycINFO literature databases, we summarized responses with lithium and controls followed by selective random-effects meta-analyses.
Results: We identified 36 reports with 39 randomized controlled trials: six for monotherapy and 12 for adding lithium to antidepressants for acute major depression, and 21 for long-term treatment. Data for monotherapy of acute depression were few and inconclusive. As an adjunct to antidepressants, lithium was much more effective than placebo ($p<0.0001$). For long-term maintenance treatment, lithium was more effective than placebo in monotherapy ($p=0.011$) and to supplement antidepressants ($p=0.038$), and indistinguishable from antidepressant monotherapy.
Conclusions: The findings indicate efficacy of lithium as a treatment for some aspects of major depressive disorder, especially as an add-on to antidepressants and for long-term prophylaxis. It remains uncertain whether some benefits of lithium treatment occur with many major depressive disorder patients, or if efficacy is particular to a subgroup with bipolar disorder-like characteristics or mixed-features.

Keywords
Lithium, unipolar major depression, systematic review

Introduction

[AQ: 3][AQ: 4][AQ: 5]Lithium is considered a standard treatment for bipolar disorder (BD) (Baldessarini 2013; Geddes et al. 2004; Goodwin et al. 2016; Yatham et al. 2018). It may also reduce risk of suicide in BD patients (Cipriani et al. 2013; Tondo et al. 2001; Tondo and Baldessarini 2015), and perhaps also in major depressive disorder (MDD) (Guzzetta et al. 2007). There also is some evidence that lithium treatment may exert protective effects on cerebral tissue and might reduce risk of dementia (Gerhard et al. 2015; Matsunaga et al. 2015), and even that it may reduce the risk of cancer in BD patients (Huang et al. 2016). Lithium also has evidence of benefit as a supplementary treatment in otherwise treatment-resistant major depression (Dold and Kasper 2017; Nelson et al. 2014).

However, the effects of lithium in the treatment of both acute or recurrent MDD remain uncertain. Most clinical trials of lithium for depression, especially soon after its modern re-introduction into medicine in 1949, included patients with a variety of recurrent major mood disorders, in whom unipolar and bipolar depression was not consistently differentiated (Adli et al. 1998), and indeed before formal distinction of the BD and MDD syndromes (DSM-III 1980). [AQ: 6] This circumstance probably reflected an assumption that depressive phases of both syndromes may respond to the same treatments–a concept which is increasingly challenged (Baldessarini 2013; Baldessarini et al. 2017, 2018; Ghaemi 2008; Pacchiarotti et al. 2013). In addition, these syndromes have significant clinical, epidemiological, and longitudinal course differences, as well as dissimilar therapeutic responses (Baldessarini 2013; Baldessarini et al. 2017; Dunn et al. 2002; Hirschfeld 2014). Indeed, insufficient distinction between depressive episodes in MDD and BD may well have impeded research and practice aimed at their optimal clinical management.

Lithium monotherapy for acute unipolar major depression

Souza and Goodwin (1991) reviewed the efficacy of lithium for the treatment of acute depression. They found some benefit from

[1]International Consortium for Mood and Psychotic Disorder Research, McLean Hospital, Belmont, USA
[2]Department of Neurology and Psychiatry, Clinica Alemana Universidad del Desarrollo, Santiago, Chile
[3]Early Intervention Program, J Horwitz-Barak Psychiatric Institute, Santiago, Chile
[4]Research Division, Institute of Mental Health/Woodbridge Hospital, Singapore
[5]Department of Psychiatry, Harvard Medical School, Boston, USA
[6]Lucio Bini Mood Disorder Centers, Cagliari and Rome, Italy
[7]Department of Psychiatry, Universidad de Los Andes, Chile[AQ: 1]
[8]Department of Psychiatry, Pontificia Universidad Católica de Chile, Santiago, Chile[AQ: 2]

Corresponding author:
Juan Undurraga, Department of Neurology and Psychiatry, Clínica Alemana Universidad del Desarrollo, Av. Vitacura 5951, Santiago, PC-7650568, Chile.
Email: juanundu@gmail.com

lithium, and clear superiority over placebo. However, they included trials with approximately 50% BD patients as well as uncontrolled studies. A later review by Adli et al. (1998), also found lithium to be an effective monotherapy for acute depression, but again included trials with MDD and BD patients, some not peer-reviewed.

Antidepressant augmentation trials

Lithium may have clinical value for depressed patients poorly responsive to antidepressant treatment (Edwards et al. 2013). Crossley and Bauer (2007) reported on two meta-analyses of the efficacy of lithium in accelerating or augmenting clinical response to antidepressants in patients with acute major depression. In five studies of hastening treatment-response, comparing lithium versus placebo added to tricyclic antidepressants yielded a nonsignificant difference (odds ratio (OR)=−0.43 (95% confidence interval (CI): –0.93 to +0.07)). In 10 studies of augmenting various antidepressants with lithium versus placebo, lithium was much more effective (OR=3.11 (95% CI: 1.80–5.37)). A major limitation, however, is that some of the trials may have included cases of bipolar depression. Bauer et al. (2010, 2014) later updated the preceding review, adding two more-recent trials and finding the same level of superiority of lithium (OR=3.11), even with less restrictive inclusion criteria, including some uncontrolled and small studies and others involving effects of discontinuing lithium augmentation.

Nelson et al. (2014) reported on a meta-analysis examining efficacy of lithium as an adjunct to tricyclic and second-generation antidepressants in nine randomized, placebo-controlled trials. They found highly significant superiority of lithium over placebo (OR=2.89 (95% CI: 1.65–5.05)). As only 13 of 237 subjects (5.49%) were diagnosed with bipolar depression, these findings appear to provide a reasonable estimate of lithium's efficacy as adjunctive therapy compared to placebo in mainly non-bipolar major depressive episodes. Nevertheless, it is noteworthy that the largest superiority of lithium over placebo (OR=12.3 (95% CI: 2.26–66.5)) was found in a small study with a high proportion of BD patients (9/27) (Schöpf et al. 1989), suggesting lesser efficacy in non-bipolar depression.

Long-term monotherapy trials

Long-term lithium monotherapy is effective in preventing recurrences of bipolar disorder (Goodwin et al. 2016; Kessing et al. 2018). A Cochrane-based systematic review considered randomized controlled trials (RCTs) comparing lithium against antidepressants for long-term, prophylactic treatment of subjects diagnosed with a major affective disorder, with an effort to exclude BD patients identified in 2/8 of the included trials (Cipriani et al. 2006). Included were 475 subjects randomly allocated to lithium or antidepressants. Participants were followed-up until relapse or for 12–36 months. Daily trough serum concentrations of lithium were 0.5–1.4 mEq/L. There was a statistically significant difference favoring lithium for fewer recurrences (RR=0.34 (95% CI: 0.14–0.82)) using fixed-effects meta-analysis, but the outcome was non-significant with more conservative random-effects modeling (RR=0.40 (95% CI: 0.14–1.18)). [AQ: 7]

Suicide prevention in MDD patients

Guzzetta et al. (2007) reported on a meta-analysis aimed at evaluating evidence of a possible antisuicidal effect of lithium in patients with unipolar MDD. They systematically reviewed available literature and obtained unpublished data from investigators. Retrieved data involved a total of 2434 person-years of exposure (1149 with lithium, and 1285 without), and found a highly significant 88.5% lower risk of suicidal acts with versus without lithium treatment (incidence rate ratio (IRR)=8.71 (95% CI: 2.1 to 77.2); pooled RR=4.24 (95% CI: 1.49–12.0)). Moreover, they found an 85% reduction in risk of completed suicide among subjects given lithium (IRR=6.77 (95% CI: 1.29–66.8).

Cipriani et al. (2005) reported on a systematic review of lithium versus suicidal behavior as well as all-cause mortality in mood disorder patients. In data pooled from 32 RCTs (with 3458 participants), lithium was effective in preventing suicide (OR=0.26 (95% CI: 0.09–0.77)), deliberate self-harm (OR=0.21 (95% CI: 0.08–0.50)), as well as death from all causes (OR=0.42 (95% CI: 0.21–0.87)). A later, updated review considered data from 48 trials (with 6674 subjects), including information about cases of unipolar MDD (Cipriani et al. 2013). Mean duration of follow-up was 19.1 (range 4–48) months. Meta-analyses confirmed overall efficacy of lithium treatment in reducing the risk of suicide with any type of mood disorder (OR=0.13 (95% CI: 0.03–0.66)) and reduction of deaths from any cause (OR=0.38 (95% CI: 0.15–0.95)), with less certain effects on risk of self-harm. For MDD considered separately, there also was reduced risk of suicide with lithium (OR=0.36 (95% CI: 0.13–0.98)), and fewer total deaths (OR=0.13 (95% CI: 0.02–0.76)), compared to placebo.

Aims of the present study

Given current gaps of knowledge and heterogeneous inclusion criteria in previous reviews, especially regarding depressed BD patients along with MDD cases, we aimed at systematically reviewing peer-reviewed reports pertaining to the efficacy of lithium in various aspects of the treatment of unipolar MDD: (a) as monotherapy for acute depression, (b) as an adjuvant treatment aimed at increasing efficacy of antidepressants generally or for treatment-resistant depression (TRD), and (c) for long-term, prophylactic treatment.

Methods

Search strategy

We sought to identify reports of randomized trials comparing lithium with placebo or other medicines used in the treatment of unipolar depression. Systematic, computerized searches of Medline, Cochrane Library, and PsycINFO research literature databases used the following search-terms: ("lithium" (MeSH Terms) OR "lithium" (All Fields)) AND ("depressive disorder" (MeSH Terms) OR ("depressive" (All Fields) AND "disorder" (All Fields)) OR "depressive disorder" (All Fields) OR "depression" (All Fields) OR "depression" (MeSH Terms)) AND ("placebos" (MeSH Terms) OR "placebos" (All Fields) OR "placebo"

(All Fields)) AND "humans" (MeSH Terms). In addition, we hand-searched published reviews and research reports for additional, relevant citations. Searching was limited to peer-reviewed reports of RCTs, reported from 1970 to January 2018 in any language, with an English or Spanish summary.

Eligibility criteria

We included reports of double-blind trials involving randomization to monotherapy (or adjunctive therapy) with lithium compared to placebo or to any other psychotropic agent, in adults, in an apparently unipolar, major depressive episode based on DSM-III to DSM-5, ICD-9 or -10, or RDC diagnostic criteria. [AQ: 8] Lithium doses could be fixed or flexible. We excluded reports involving special populations, such as juveniles, persons with major general medical or neurological illnesses, or including ⩾15% with bipolar depression or other psychiatric diagnoses (but, included trials with more BD cases if outcomes for unipolar depression subjects were reported separately). We defined short-term treatment of acute depression as trials of at least one and <12 weeks, and "long-term" as trials with ⩾12 weeks follow-up.

Outcome measures

We defined response in short-term trials of major depressive episodes, as showing ⩾50% reduction in depressive symptoms, as defined by the authors, typically based on scores on well-established rating-scales. We also considered percentage change in depression scores from baseline to endpoint, when possible. Longer-term trials had highly heterogeneous definitions of outcomes, but we considered response as the proportion of patients without new depressive episodes (as defined by the authors) during follow-up.

Data analysis

Data were tabulated and pooled, usually as means with 95% CIs. We employed random-effects meta-analysis to compare responses between subjects treated with versus without lithium, and reported a pooled OR. Data from adjunctive trials and from long-term trials were subjected to meta-regression modeling following meta-analysis. Statistical software included Statview.5 (SAS Institute, Cary, North Carolina, USA) for spreadsheets, and STATA.13 (StataCorp, College Station, Texas, USA) for analyses.

Results

Electronic searching yielded 1296 potentially relevant studies, and we identified 16 additional reports by hand-searching published reports and reviews (total of 1312 records). We assessed 73 full-text reports for possible study inclusion. Of these, we excluded 22 for having >15% BD in the sample, eight for giving insufficient information, three for being uncontrolled, two for being duplicated, and two for other reasons, leaving a total of 36 reports of 39 RCTs for analysis (six for short-term treatment of acute major depression, 12 for short-term augmentation treatment, and 21 for long-term maintenance treatment) (see Figure 1 and Supplementary Material Appendix References).

Lithium monotherapy for acute unipolar major depressive episodes

For analysis of lithium monotherapy in acute unipolar major depression, we included six RCTs comparing lithium to placebo (two trials) or to a different drug (three trials compared with tricyclic antidepressants (TCAs)), and one with serotonin reuptake inhibitor (SSRI) antidepressant), with a total of 218 patients, 76.3% of whom were women. Follow-up was 2–6 weeks and only one trial was not under double-blind conditions (Bschor et al. 2013), [AQ: 9] but is included as such trials are rare. We found no difference between lithium and its comparator (another drug or placebo) in response as defined by in the reports analyzed. We also did not find differences in percentage change in depression symptom ratings between intake and endpoint. The lack of difference between treatment with lithium versus placebo (only two trials) indicates a lack of efficacy, so that a lack of difference from antidepressants may not mean that lithium yielded equivalent effects.

Lithium augmentation of antidepressants for acute unipolar major depression

We included 12 RCTs of lithium versus placebo, as adjuncts to antidepressants for acute unipolar major depression. There were 541 patients (240 randomized to lithium, 301 to placebo or a very low dose of lithium), followed-up for a mean of 3.50 weeks. Overall, random-effects meta-analysis found a highly significant pooled outcome (OR 2.34 (95% CI: 1.57–3.51), $p<0.0001$) favoring lithium over placebo as an adjunct to antidepressants (Figure 2). The estimated number needed to treat (NNT; or number subjects to be treated to prevent one additional undesirable outcome) was moderate (4.9 (95% CI: 3.3–9.2)). Of note, however, only 4/12 studies, individually, found significant benefits of adding lithium. Furthermore, in nine trials involving TRD (involving failure of at least one trial of a standard antidepressant at a clinically plausible dose and time) yielded a highly significant superiority of lithium over placebo (OR=3.09 (95% CI 1.74–5.51), $p<0.0001$). No tested factor (Table 1) was significantly associated with outcome in meta-regression modeling, and funnel plot (study-size versus OR) did not indicate reporting bias.

Long-term trials

We identified 21 RCTs from 18 reports (three reports with two active-treatment or control arms each) reporting on long-term treatment with lithium for unipolar MDD, either as monotherapy versus placebo (seven trials) or antidepressant (five trials) or as an adjunct to antidepressant treatment (nine trials). They involved 846 patients randomized to lithium (n=432) (alone or as an add-on) or a comparator (n=414) and followed-up for a mean of 22.2 (95% CI: 17.4–27.0) months; 70.7% of subjects were women. Random-effects meta-analysis of all 21 studies yielded an overall pooled OR of 2.80 ((95% CI: 1.59–4.92); $p<0.0001$) favoring lithium over placebo or other comparators. No tested factor (Table 2) was significantly associated with outcome in meta-regression modeling, and funnel plot did not indicate reporting bias.

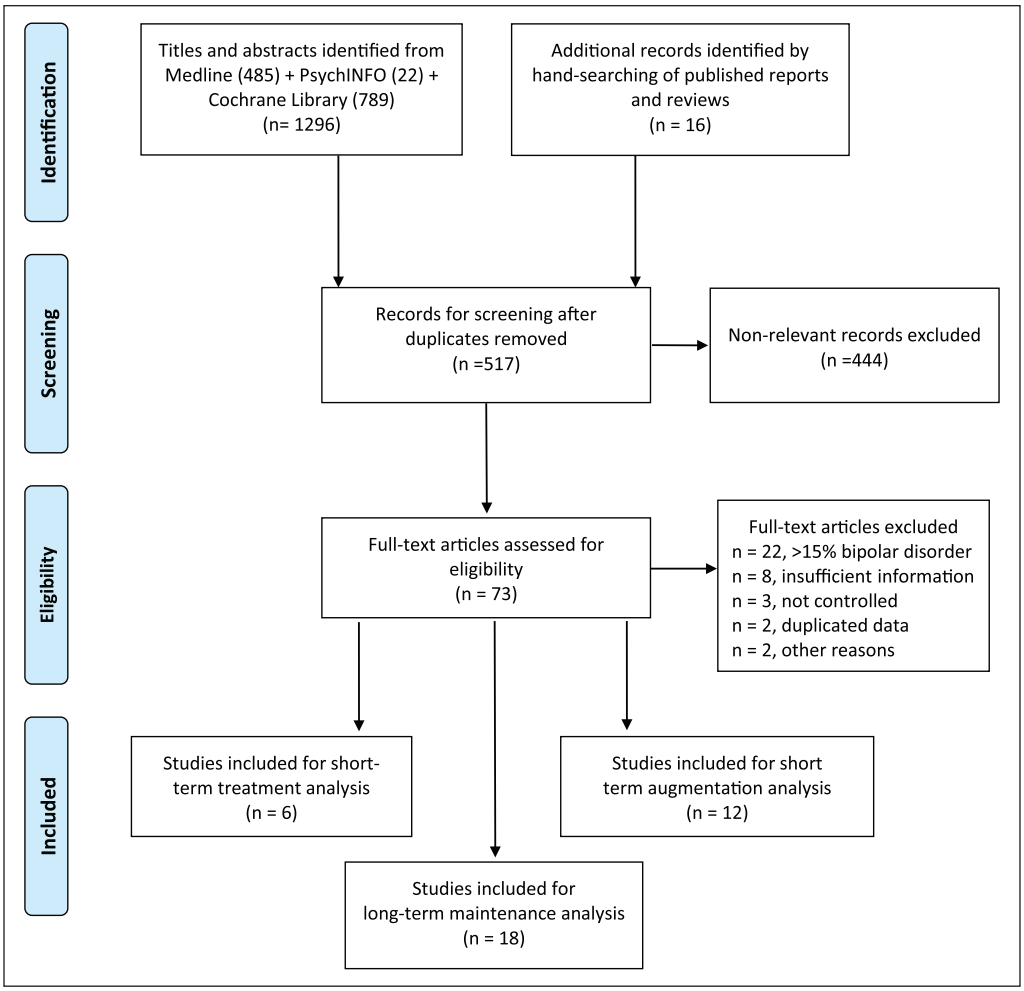

Figure 1. [AQ: 16] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report-selection flow diagram. Lithium monotherapy for acute unipolar major depression. Source: Moher et al. (2009). [AQ: 17]

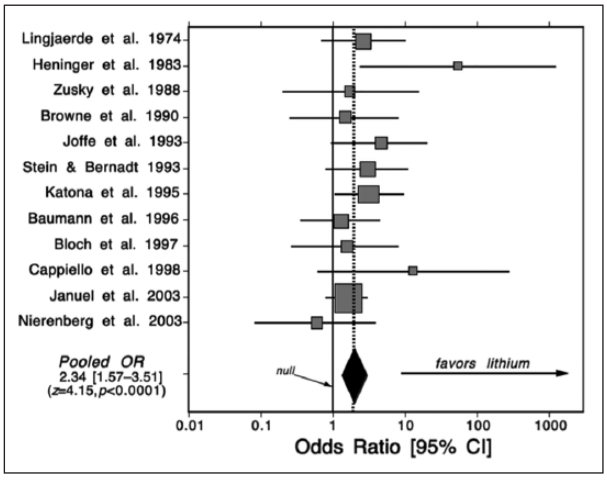

Figure 2. Random-effects meta-analysis of effects of lithium vs placebo to supplement antidepressant treatment for otherwise unresponsive acute major depression in 12 trials, based on data in Table 1. Size of squares is proportional to weight of each trial. Pooled odds ratio (OR)=2.34 (95% confidence interval (CI): 1.57–3.51) (z=4.15, p<0.0001).

Of note, by meta-analysis, lithium proved to be more effective than placebo in seven trials (OR=4.51 ((95% CI: 1.41–14.5), p=0.011; Figure 3). Additional meta-analyses indicated a nonsignificant difference between lithium and antidepressant monotherapy in five trials (OR=2.21 (95% CI: 0.69–7.10); p=0.024), and found lithium to be effective as an adjunct to antidepressants in nine trials (OR=2.38 (95% CI: 1.05–5.40), p=0.038; Table 2).

In addition, meta-analyses of seven trials that involved discontinuing lithium or antidepressants yielded a nonsignificantly larger effect-size for the discontinued treatment (OR=4.61 (95% CI: 1.21–17.4), p=0.025) than in 14 other trials not involving treatment-discontinuation (OR=2.39 (95% CI: 1.27–4.50), p=0.004). This outcome suggests that there was not more than a small effect of treatment-discontinuation itself.

Discussion

We found inadequate data to evaluate the efficacy of lithium compared either to placebo or antidepressants in acute, unipolar, major depressive episodes (Table 3), although another

Table 1.[AQ: 13] Lithium as an adjunct to antidepressants in acute major depression.

Study, year	Diagnosis	Treatment	Duration (weeks)	Response rate (% of subjects)		Odds ratio (95% CI)
				+Lithium	+Placebo	
Lingjaerde et al., 1974	MDD (not TRD)	TCAs	6.0	40.0 (8/20)	20.0 (5/25)	2.67 (0.71–10.1)
Heninger et al., 1983	MDD (TRD)	TCAs, MIA	2.0	62.5 (5/8)	0.00 (0/17)	55.0 (2.44–1238)[a]
Zusky et al., 1988	MDD (TRD)	TCAs, MAOIs	3.0	37.5 (3/8)	25.0 (2/8)	1.80 (0.21–15.4)
Browne et al., 1990	MDD (TRD)	TCAs	2.0	26.7 (4/15)	20.0 (3/15)	1.45 (0.26–8.01)
Joffe et al., 1993	MDD (TRD)	TCAs	2.0	52.9 (9/17)	18.8 (3/16)	4.88 (1.01–23.6)[a]
Stein and Bernadt, 1993	MDD (TRD)	TCAs[b]	3.0	43.8 (7/16)	20.6 (7/34)	3.00 (0.82–10.9)
Katona et al., 1995	MDD (TRD)	FLX, LFP	6.0	51.7 (15/29)	25.0 (8/32)	3.21 (1.09–9.48)[a]
Baumann et al., 1996	MDD (TRD)	CTP	1.0	60.0 (6/10)	25.0 (8/32)	4.50 (1.01–20.1)[a]
Bloch et al., 1997	MDD (not TRD)	DMI	5.0	75.0 (9/12)	66.7 (10/15)	1.50 (0.28–8.14)
Cappiello et al., 1998	MDD (TRD)	DMI	4.0	28.6 (4/14)	0.00 (0/15)	13.3 (0.65–274)
Januel et al., 2003	MDD (not TRD)	CMI	2.0	56.8 (42/74)	45.3 (34/75)	1.58 (0.83–3.02)
Nierenberg et al., 2003	MDD (TRD)	NTR	6.0	11.1 (2/18)	17.6 (3/17)	0.58 (0.08–4.01)
Pooled (12 trials) (with 95% CI)	**All MDD, 9 TRD**	**10 TCAs, 2 SRIs**	**3.50 (2.34–4.66)**	**113/240, 47.1% (40.6–53.6)**	**83/301, 27.6% (22.6–33.0)**	**Pooled OR=2.34 (1.57–3.51)[c]**

AMI: amitriptyline; CI: confidence interval; CMI: clomipramine; CTP: citalopram; DMI: desipramine; FLX: fluoxetine; LFP: lofepramine; MAOIs: monoamine oxidase inhibitors; MDD: major depressive disorder; MIA: mianserin; OR: odds ratio; NNT: number needed to treat; NTR: nortriptyline; SRI: serotonin-reuptake inhibitor; TCA: tricyclic-type antidepressant; TRD: treatment-resistant depression (having failed at least one seeming adequate trial of an antidepressant).
Treatments: AMI, CMI, CTP, DMI, FLX, LFP, MAOIs, MIA, NTR, other treatments, notably antipsychotics; SRIs, TCAs. Of note, the nine trials involving lithium to rescue patients with antidepressant-resistant depression yielded a meta-analytically pooled OR=3.08 (95% CI: 1.83–5.19) (z=4.22, $p<0.0001$), and the three trials involving supplementation of antidepressant treatment yielded a pooled OR=1.72 (95% CI: 0.99–2.98) (z=1.95, p=0.05).
[a]Only 4/12 trials (33.3%), individually found significant benefits of lithium. Two other studies (without reported response rates) also found no significant benefit of adding lithium to an antidepressant (Nick et al., 1976; Shelal et al., 1996), as did a third with only two days of treatment (Kantor et al., 1966).
[b]Controls include response to placebo or a probably ineffectually low dose of lithium carbonate (250 mg/day).
[c]Based on random-effects meta-analysis (with low heterogeneity: I^2=3.17%); pooled OR=2.34 (95% CI: 1.57–3.51) (z=4.15, $p<0.0001$; NNT=4.9 (95% CI: 3.3–9.2); see Figure 2).

mood-stabilizing agent, carbamazepine, may be effective (Zhang et al. 2008). However, lithium was effective as an adjunctive treatment to augment responses to antidepressants for acute major depressive episodes, including cases of TRD, with an overall OR of 2.34, $p<0.0001$), though only 4/12 individual trials individually found significant superiority for lithium (Table 1). Only two trials tested lithium with a specific modern antidepressant (citalopram, fluoxetine); both found significant benefit with added lithium (Table 1). The conclusion that lithium is effective as an adjunct to antidepressants, including for TRD, accords with earlier reviews (Abou-Saleh et al. 2017; Bauer et al. 2010, 2014; Nelson et al. 2014; Rush et al. 2009; Zhou et al. 2015).

Particularly interesting findings emerged from meta-analyses of 21 long-term, controlled trials aimed at preventing recurrences in MDD (Table 2; Figure 3). Notably, lithium was superior to placebo in seven long-term trials (OR=4.51, p=0.011), as well as an augmenting treatment added to antidepressants in nine long-term trials (OR=2.38, p=0.038), and did not differ from long-term treatment with antidepressants alone in five trials (OR=2.21, p=0.18). Since long-term antidepressant treatment has abundant controlled trial-based evidence of effectiveness in recurrent MDD (Sim et al. 2015), the lack of difference between lithium and antidepressants suggests that they may be similarly effective for prophylaxis against MDD. These findings are consistent with a finding of reduced risk of psychiatric hospitalization among MDD patients treated with lithium in a Finnish national sample (Tiihonen et al. 2017). Also of note, the long-term effects of lithium treatment did not appear to be accounted for by artifactual clinical worsening by treatment-discontinuation (Baldessarini 2013; Faedda et al. 1993).

Overall, the present findings support the possible value of lithium as an adjunct to antidepressants for both acute depression and for its prophylaxis, but leave lithium inadequately tested as a monotherapy for acute, unipolar major depression, as is also the case regarding acute bipolar depression (Selle et al. 2013). A critical question is whether benefits of lithium treatment in non-bipolar depression represent a modest general effect, or one that is particular to depressed patients with some bipolar-like characteristics. Such cases may include those formerly considered to have "pseudounipolar" depression (Dyson and Mendels 1968), later as members of a "bipolar spectrum" with only mild hypomanic features (Akiskal 2007), and more recently considered to have depression with "mixed features" (Tondo et al. 2018; Vázquez et al. 2018), as well as depressed, later-diagnosed BD patients who have not yet presented with hypomania or mania.

Despite lithium's efficacy for the treatment of affective disorders and possible reduction of suicidal risk and general mortality based on evidence including from randomized, placebo-controlled, trials, lithium is underutilized (Baldessarini 2013; Baldessarini et al. 2006; Post 2018). Possible reasons for this neglect include, first, concern about the safety of lithium due to its narrow therapeutic index and required routine monitoring of serum concentrations of

Table 2.[AQ: 14] Long-term, randomized, controlled maintenance trials of lithium treatment for unipolar major depressive disorder.

Study	Treatment	Comparator	Mean lithium level (mEq/L)[a]	Duration (weeks)	Lithium discontinued	Female (%)	Response rate (% of subjects)		Odds ratio (OR (95% CI))
							Lithium	Comparator	
Baastrup et al., 1970	Li	Pbo	1.05	20	Yes	100	100 (17/17)	47.1 (8/17)	39.1 (2.03–755)[b]
Coppen et al., 1971	Li	Pbo	1.00	112	No	73	90.1 (10/11)	20.0 (3/15)	40.0 (3.58–477)[b]
Cundall et al., 1972	Li	Pbo	0.85	52	Yes	67	25.0 (1/4)	50.0 (2/4)	0.33 (0.02–6.65)
Prien et al., 1973	Li	Pbo	0.80	104	No	44	66.7(18/27)	23.1 (7/26)	6.45 (1.95–21.3)[b]
Prien et al., 1973	Li	IMI	0.80	104	No	44	66.7 (18/27)	68.0 (17/25)	1.12 (0.34–3.63)
Coppen et al., 1976	Li	MPT	1.00	56	Yes	73	75.0 (9/12)	25.0 (2/8)	9.00 (1.14–71.0)[b]
Fieve et al., 1976	Li	Pbo	—	15	No	89	42.9 (6/14)	35.7 (5/14)	1.35 (0.29–6.18)
Coppen et al., 1978	Li	MIA	1.00	78	Yes	61	100.0 (15/15)	46.2 (6/13)	35.8 (1.77–723)[b]
Kane et al., 1982	Li	Pbo	1.00	104	No	63	71.4 (5/7)	0.00 (0/6)	28.6 (1.12–723)[b]
Kane et al., 1982	Li+IMI	IMI	1.00	104	No	63	87.5 (7/8)	16.7 (1/6)	35.0 (1.74–703)[b]
Glen et al., 1984	Li+AMI	AMI	0.90	156	No	79	30.4 (17/56)	31.9 (15/47)	0.93 (0.40–2.15)
Prien et al., 1984	Li	Pbo	0.66	104	Yes	67	27.0 (10/37)	20.6 (7/34)	1.43 (0.47–4.31)
Prien et al., 1984	Li+IMI	IMI	0.66	104	No	67	47.4 (18/38)	51.3 (20/39)	0.86 (0.35–2.09)
Johnstone et al., 1990	Li+AMI	AMI	0.70	156	No	89	64.3 (9/14)	69.2 (9/13)	0.80 (0.16–3.99)
Franchini et al., 1994	Li	FVX	0.70	104	No	84	75.0 (24/32)	87.5 (28/32)	0.43 (0.11–1.60)
Greil et al., 1996	Li	AMI	0.59	130	No	72	72.4 (21/29)	48.4 (15/31)	2.80 (0.95–8.22)
Hardy et al., 1997	Li+AD	Pbo+AD	0.40	104	Yes	83	66.7 (4/6)	66.7 (4/6)	1.00 (0.09–11.0)
Bauer et al., 2000	Li+AD	AD	0.69	20	Yes	60	100 (14/14)	53.3 (8/15)	32.9 (1.66–651)[b]
Sackeim et al., 2001	Li+NTP	NTP	0.59	24	No	66	60.9 (14/23)	40.0 (10/25)	2.33 (0.73–7.43)
Wilkinson et al., 2002	Li+AD	AD	0.43	104	No	65	96.0 (24/25)	66.7 (16/24)	12.0 (137–105.)[b]
Kok et al., 2007[c]	Li+AD	PNZ	0.90	110	No	76	46.7 (7/15)	7.14 (1/14)	11.4 (1.17–110)[b]
Mean (95% CI)	**21 comparisons in 18 reports**		**0.79 (0.69–0.88)**	**88.8 (69.6–108)**	**7/21 "enriched"**	**70.7 (64.4–77.0)**	**270/432[d] 62.5% (57.7–6)7.1**	**184/414[d] 44.4% (39.6–4)9.4**	**Pooled OR 2.80 (1.59–4.92)[d]**

AD: antidepressant; AMI: amitriptyline; CI: confidence interval; FVX: fluvoxamine; IMI: imipramine; Li: lithium; MIA: mianserin; MPT: maprotiline; NNT: number needed to treat; NTL: nortriptyline; OR: odds ratio; Pbo: placebo; PNZ: phenelzine.

Enriched trials compared continuation of an initial treatment (usually in an acute index episode) to discontinuation or change to another comparison treatment.

[a]Mean daily trough serum lithium concentrations are as provided in reports or estimated from information provided in them.

[b]Only 10/21 trials (47.6%), individually, found lithium to be significantly superior to comparison treatments, including 4/7 vs placebo (Figure 3).

[c]Kok et al., 2007 is randomized but not blinded.

[d]The pooled rates shown strongly favored lithium overall by 1.41-fold (62.5% vs 44.4% response; χ^2=27.7, $p<0.0001$). By random-effects meta-analysis, the overall OR (2.80 (1.59–4.92)) in the 21 trials strongly favored lithium (z=3.56, $p<0.0001$) with considerable heterogeneity (I^2=60.3%); NNT=3.8 (2.6–7.1). Additional random-effects meta-analyses of long-term trials considered: (a) lithium vs placebo (seven trials, OR=4.51 (1.41–14.5), z=, 2.73, p=0.011; I^2=61.8%; NNT=2.8 (1.7–8.1); see Figure 3); (b) lithium vs antidepressants (five trials, OR=2.21 (0.69–7.10), z=1.33, p=0.18; I^2=66.0%); (c) lithium+antidepressants vs antidepressants (nine trials; OR=2.38 (1.05–5.40), z=2.07, p=0.038; I^2=57.5%); (d) in seven Li-discontinued "enriched" trials (OR=4.61 (1.21–17.4)), z=2.25, p=0.025; I^2=56.4% vs 14 non-enriched trials (OR=2.39 (1.27–4.50)), z=2.71, p=0.007; I^2=62.8% (these outcomes did not differ significantly). By meta-regression, based on meta-analysis of all 21 trials, year of reporting, trial size, type of comparison treatment, duration, percentage of women, and mean lithium concentration were not associated with outcome (effect-size (OR)).

lithium and of endocrine and renal functions, with particular long-term concerns about weight gain, hypothyroidism, hyperparathyroidism, reduced urinary-concentrating ability and declining creatinine clearance (Shine et al. 2015; Tondo et al. 2017). Second, there may be a "stigmatizing" effect of lithium treatment for some patients and families, compared to other frequently used drugs such as antidepressants (Baldessarini 2013). Third and importantly, as an unpatentable mineral there is little commercial interest in lithium compared to other agents, with much less support for research and marketing (Baldessarini 2013). Despite these circumstances, lithium retains a major position among treatments for BD internationally and tends to be used for longer periods than most alternatives (Baldessarini et al., 2013). **[AQ: 10]**

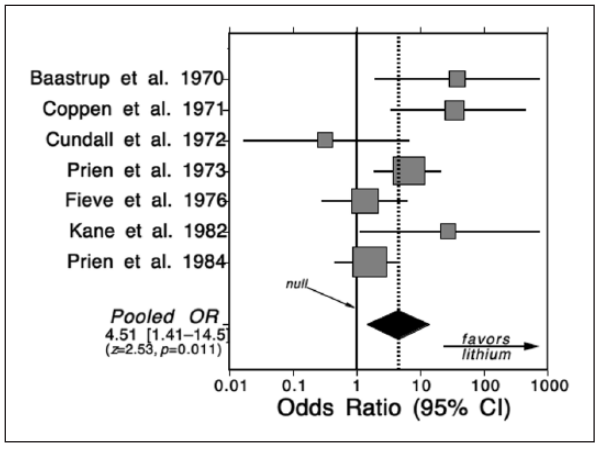

Figure 3. Random-effects meta-analysis of effects of lithium vs placebo for long-term maintenance treatment of recurrent major depressive disorder in seven trials, based on data in Table 2. Size of squares is proportional to weight of each trial. Pooled odds ratio (OR)=4.51 (95% confidence interval (CI): 1.41–14.5) (z=2.73, p=0.011).

Study limitations

Data available for some analyses were quite limited, reflecting the infrequent clinical use of lithium in the treatment of unipolar MDD, and trials varied greatly in methods. Substantial levels of heterogeneity across trials of similar type (most I^2 values >60%) led to routine reliance on relatively conservative random-effects meta-analyses. We strove to exclude studies with bipolar depressed subjects, but small proportions with BD or future (hypo)mania may have been included. Some comparisons failing to distinguish effects of treatment with lithium or alternatives (usually antidepressants), without a placebo condition for comparison, leave ambiguity as to whether lithium was as effective as the alternative, or if both treatments were ineffective. This problem appears to be less of concern among the sub-group analyses of long-term treatment (Table 2).

Conclusion

The available data were not adequate to evaluate the effectiveness of lithium monotherapy in acute unipolar major depressive episodes. However, the findings reviewed do support the probable value of lithium as an adjunct to antidepressants, notably for otherwise treatment-resistant major depression. Nevertheless, few add-on trials involve modern antidepressants, which require further assessments of effects adding lithium. Lithium also emerged as effective for prophylaxis against recurrences of depression in MDD, both in comparison to placebo and as an adjunct to antidepressants. It is not certain to what extent the effects found may reflect benefits to MDD patients broadly, or particularly to a subgroup with bipolar-like characteristics. Overall, the present findings support the possibility that lithium may have value in the treatment of nonbipolar major depression, particularly adjunctively with antidepressants and for long-term mood-stabilization.

Table 3. Lithium versus other monotherapies for acute unipolar major depression. **[AQ: 15]**

Study, year	Lithium level (mEq/L)	Comparator	Duration (weeks)	Response rate[a] (% of subjects)		Depression score improvement (% change from baseline)	
				Lithium	Comparator	Lithium	Comparator
Baron et al., 1975	0.87	Placebo	2	30.0 (3/10)	28.6 (4/14)	na	na
Watanabe et al., 1975	0.41	Imipramine	5	63.6 (7/11)	50.0 (5/10)	78.6	77.8
Khan et al., 1981	na	Amitriptyline	3	na	na	70.9	78.4
Khan et al., 1987	0.75	Placebo	6	na	na	53.2	62.1
Linder et al., 1989	0.92	Clomipramine	4	na	na	86.5	63.2
Bschor et al., 2013	0.82	Citalopram	4	50.0 (15/30)	71.9 (23/32)	49.1	60.8
Mean (95% CI)	**0.74 (0.37–1.10)**	**Various**	**4.00 (2.04–5.96)**	**49.0%**	**57.1%**	**67.7 (47.6–87.7)[b]**	**68.5 (57.5–79.4)[b]**

CI: confidence interval; na: information not available.
All trials were double-blind except Bschor et al. (2013).
[a]Response is decrease in Hamilton Depression Rating Scale (HDRS) score >50% by Watanabe et al. (1975) and Bschor et al. (2013); and as ⩾2 points improvement in the Bunney-Hamburg global rating scale (Bunney and Hamburg, 1963) after lithium administration by Baron et al. (1975).
[b]Overall difference in improvement does not differ (t=0.10, p=0.54), but only one trial (Khan et al., 1987) provided outcome data for lithium vs placebo, leaving it ambiguous whether lithium and antidepressants had similar effects or both were ineffective overall.

Declaration of conflicting interests

No author or their immediate family member has financial relationships with commercial organizations that might appear to represent potential conflicts of interest in the material presented.

Funding [GQ: 2]

This study was supported in part by CONICYT PIA ACT1414; FONDECYT 1160736, 1180358, and a research grant from Clínica Alemana de Santiago (to JU); a grant from Aretaeus Association (to LT), and a grant from the Bruce J. Anderson Foundation and by the McLean Private Donors Psychopharmacology Research Fund (to RJB). [AQ: 11]

ORCID iDs [GQ: 3]

Juan Undurraga https://orcid.org/0000-0001-6958-2369

Ariel Gorodischer https://orcid.org/0000-0001-9976-2723

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