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Efficacy and safety of lithium and lamotrigine for the maintenance treatment of clinically stable patients with bipolar disorder: A systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials with an enrichment design

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Abstract

Aim: Whether patients with adult bipolar disorder (BD) who have been clinically stabilized with lithium or lamotrigine should continue this medication is not established fully. This systematic review and meta-analysis evaluated the efficacy and safety of lithium and lamotrigine for maintenance treatment in clinically stable patients with adult BD.

Methods: This meta-analysis included only double-blind, randomized, placebo-controlled trials with an enrichment design that selected patients who responded acutely to lithium or lamotrigine. Reports prior to November 15, 2018, were retrieved from the PubMed/Cochrane Library/Embase. The primary outcome was the relapse rate

Oya and Sakuma equally contributed to this study.

due to any mood episode at the study endpoint. Other outcomes were relapse rates due to a manic/hypomanic/mixed episode or depression at the study endpoint, discontinuation rate, death, and death by suicide. Risk ratios (RRs) (95% confidence intervals) were calculated. When the random-effects model showed significant differences between groups, the number-needed-to-treat (NNT) was estimated.

Results: The search retrieved two studies regarding lithium (N = 218) and four evaluating lamotrigine (N = 706). Both drugs were superior to placebo for reducing the relapse rate due to any mood episode [lithium: RR = 0.52 (0.41-0.66), $P < 0.00001$, $I^2 = 0\%$, NNT = 2.3 (1.6-4.2); lamotrigine: RR = 0.81 (0.70-0.93), $P = 0.004$, $I^2 = 0\%$, NNT = 8.3 (5.0-25.0)] and all-cause discontinuation. There were no significant differences in other outcomes between lithium or lamotrigine and the placebo groups.

Conclusion: Both drugs showed benefit for preventing relapse in clinically stable patients with adult BD. However, the number of studies and patients in this analysis was small.

KEYWORDS

bipolar disorder, lamotrigine, lithium, meta-analysis, systematic review

1 | INTRODUCTION

Patients with bipolar disorder (BD)[1] repeatedly and irregularly present mania/hypomania or depression during their life course, which can result in social and occupational disability.[2] A meta-analysis of mood stabilizer usage[3] reported that continuing their use significantly reduced the relapse rate for adult BD patients [risk ratio (RR) = 0.68, 95% confidence intervals (95%CI) = 0.60-0.77, $P < 0.001$], and therefore, recent treatment guidelines for BD have recommended their continuation for a long period, even after remission.[4,5] A network meta-analysis of randomized controlled trials (RCTs) investigated the comparative efficacy and safety of pharmacological treatments for BD and suggested that lithium should be used as the first-line treatment for preventing relapse in patients with this disorder.[6] However, that meta-analysis included both RCTs with an enrichment design (ie which selected patients who had responded acutely to lithium) and those without an enrichment design (ie which included patients who had responded acutely to drugs other than lithium or who had not received any treatment prior to the study).[6] Consequently, that analysis did not directly establish whether patients with adult BD clinically stabilized by taking lithium should continue with this medication, and, unfortunately, this important clinical question remained unanswered.

Therefore, we conducted a systematic review and meta-analysis that included only double-blind randomized placebo controlled trial (DBRPCTs) with an enrichment design for lithium having the aim of evaluating its efficacy and safety for the maintenance treatment of clinically stable patients with adult BD. Since only lamotrigine has been approved for the maintenance treatment of adult patients with BD in Japan, consequently, we conducted an additional systematic review and meta-analysis that included only DBRPCTs with an enrichment design for lamotrigine.

2 | METHODS

2.1 | Inclusion criteria and search strategy

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[7] and the PRISMA checklist is presented below in the Supplementary Appendix. Before beginning the study, we registered its protocol on the PROSPERO database of systematic reviews (lithium: CRD42018114563; lamotrigine: CRD42018117399).

We included only DBRPCTs with an enrichment design that selected patients who had responded acutely to lithium or to lamotrigine. Our systematic literature review used the following strategy: Patients-Intervention-Comparator-Outcome. The patients were adults with BD that had been clinically stabilized by taking lithium/lamotrigine; the intervention was a continuation of the lithium/lamotrigine treatment; the comparator was placebo; and the outcomes were efficacy and safety, as detailed in the following section.

Miura et al.'s network meta-analysis,[6] described earlier, had already identified six DBRPCTs related to our strategy: two for lithium[8,9] and four for lamotrigine.[10–13] That study's final search date was June 28, 2013; therefore, we started our search period at January 1, 2013 (to provide a short period of overlap with Miura et al.'s study), and we accepted reports published up to November 15, 2018. Relevant studies were identified through searches of the PubMed, Cochrane Library, and Embase databases, using the search terms "(bipolar OR affective) AND (maintenance, prophylaxis, recurrence, relapse, admission, OR prevent*) AND (lithium OR lamotrigine)." There was no language restriction. Additional eligible studies were also sought by examining the reference lists of the primary articles and relevant reviews. At least two of our

TABLE 1 Study, patient, and treatment characteristics of the included double-blinded, randomized placebo-controlled trials of patients with bipolar disorder

	(1) Study, (2) total n, (3) country, (4) sponsorship, (5) design	(1) Diagnosis, (2) patients status, (3) analyzed population	Duration of study (wk)	Drug (mg/d)	Randomized n	Age (mean ± SD, y)	Duration of illness (mean ± SD, y)	Male (%)	Race (%)	Concomitant drugs (%)	Relapse rate due to any mood episode (%)
LIT studies	(1) Cundall 1972, (2) 13, (3) UK, (4) industry, (5) DBRPCT (crossover design)	(1) BD[a] (NR), (2) 1 y ≤ stabilized periods ≤ 3 y, (3) ITT	26	LIT 250 (Fi)[b]	8	50.8	NR	37.5	NR	NR	37.5[c,d]
				PLA	5	58.8		40.0			100.0[c,d]
	(1) Prien 1973, (2) 205, (3) USA, (4) industry[e], (5) DBRPCT	(1) BD (NR), (2) age ≤ 60 y, (3) ITT	104	LIT 1000 (median)[f]	101	44 (median)	NR	64.9	NR	NR	42.6[c]
				PLA	104						80.8[c]
LAM studies	(1) Bowden 2003, (2) 175, (3) USA, (4) industry, (5) DBRPCT	(1) BD I (DSM-IV), (2) age ≥ 18 y, CGI-S ≤ 3 (3) ITT (LOCF)	76	LAM (100-400)	59	40.6 ± 12.6	NR	44.8	NR	CHL (NR), LOR (NR), TEM (NR), OXA (NR)	47.5[c]
				PLA	70	40.9 ± 11.0		49.3			70.0[c]
	(1) Calabrese 2000, (2) 182, (3) USA, (4) industry, (5) DBRPCT	(1) BD I, BD II (DSM-IV), (2) age ≥ 18 y, with rapid cycling, (3) ITT (LOCF)	26	LAM (100-500)	93	38.5	NR	44.6	NR	LOR (NR)	48.4[c]
				PLA	89	37.4		40.9			55.1[c]
	(1) Calabrese 2003, (2) 413[g], (3) USA, (4) industry, (5) DBRPCT	(1) BD I (DSM-IV), (2) age ≥ 18 y, (3) ITT (LOCF)	76	LAM 50, 200, 400 (Fi)	171[g]	44.1 ± 11.7[g]	NR	41.4[g]	NR	CHL (NR), LOR (NR), TEM (NR), OXA (NR), MID (NR)	48.5[c,d]
				PLA	121	42.1 ± 13.0		50.4			54.5[c]
	(1) Koyama 2011, (2) 103, (3) Japan, (4) industry, (5) DBRPCT	(1) BD I (DSM-IV-TR), (2) age ≥ 20 y, CGI-S ≤ 3, compliance rate ≥ 70%, (3) ITT	26	LAM 200 (Fi)	45	42.4 ± 11.8	NR	40.0	NR	TRI (NR), ZOP (NR)	44.4
				PLA	58	43.1 ± 12.7		46.6			63.8

BD (I, II), bipolar (I, II) disorder; CGI-I (-S), the Clinical Global Impressions-Improvement (-Severity); CHL, chloral hydrate; d, day(s); DBRPCT, double-blind, randomized, placebo-controlled trial; DSM (-IV, -TR), Diagnostic and Statistical Manual of Mental Disorders (-Fourth Edition, -Text Revision); Fi, fixed dose; ITT, intention-to-treat; LAM, lamotrigine; LIT, lithium; LOCF, last observation carried forward; LOR, lorazepam; MID, midazolam; n, number of patients; NR, not report; OXA, oxazepam; PLA, placebo; SD, standard deviation; TRI, triazolam; TEM, temazepam; UK, United Kingdom; USA, United States of America; wk, week(s); y, year(s); ZOP, zopiclone.

[a]Patients diagnosed with recurrent depressive were excluded from this meta-analysis.

[b]The plasma LIT concentration was 0.5-1.2 mEq/L.

[c]We extracted the data from the following Miura's article. Miura T et al.[6]

[d]The data before crossover.

[e]Lithium carbonate was supplied by John Buckley of Smith Kline & French Laboratories, Philadelphia.

[f]The median serum LIT concentration was 0.7 mEq/L.

[g]Although there was LAM 50 mg/d arm in this study, because this dose was considered to be lower therapeutic dose, we did not include data from the arm in our meta-analysis.

eleven authors (KO, KS, SE, YH, MH, YMatsuda, YMatsui, NM, IN, MO, and TK) independently assessed the selected studies based on the inclusion/exclusion criteria. Each of the identified studies was checked against the inclusion and exclusion criteria and any discrepancies in coding were resolved by discussion among the authors.

2.2 | Outcomes

We included the outcome measures of at least two studies for each outcome measure. The primary outcome was the study-defined relapse rate due to any mood episode at the study endpoint. Other outcomes were a manic/hypomanic/mixed or depressive episode, all-cause discontinuation, discontinuation due to adverse events, death, and death by suicide.

2.3 | Data extraction

The authors independently extracted data from the included studies. An intention-to-treat or a modified intention-to-treat analysis was applied. When data required for the meta-analysis were missing, we contacted the study investigators and requested their unpublished data or we extracted data regarding a death in a lithium study[9] from a previous review article.[14]

2.4 | Statistical analysis

The meta-analyses were conducted using Review Manager,[15] and for each one the RR (with 95%CI) was calculated. When the random-effects model showed significant differences between groups, the number-needed-to-treat or number-needed-to-treat-harm (NNT and NNH, respectively) was estimated. Heterogeneity was evaluated using the I^2 statistic, with $I^2 \geq 50\%$ considered to indicate considerable heterogeneity.[16] The methodological quality of the trials was assessed using the Cochrane risk of bias criteria. We did not explore potential publication bias because our analysis included fewer than the 10 studies needed to use the funnel plot method.[16]

3 | RESULTS

3.1 | Study characteristics

Searches of the PubMed, Cochrane Library, and Embase databases yielded 597, 275, and 437 reports, respectively. We excluded 1219 of these studies based on the title or abstract, 86 after reading the full text, and four because they were duplicates. Consequently, and remarkably, although we searched and checked reports published since 2013, not one met our inclusion criteria. However, Miura et al.'s study[6] identified two DBRPCTs for lithium[8,9] (mean duration, 65 weeks; N = 218) and four for lamotrigine[10–13] (51 weeks; N = 706) (Figure S1). Table 1 summarizes the characteristics of these studies. Figure S2 addresses the risk of bias assessment.

3.2 | Lithium vs placebo

The meta-analysis showed that lithium was superior to placebo for reducing the relapse rate due to any mood episode [RR = 0.52, 95%CI = 0.41-0.66, $P < 0.00001$, $I^2 = 0\%$, NNT = 2.3 (1.6-4.2)] and regarding all-cause discontinuation (RR = 0.57, 95%CI = 0.47-0.69, $P < 0.00001$, $I^2 = 0\%$, NNH = 2.3 (1.6-4.3)) (Figure S3). If the control event rate (CER, a relapse rate in the control group) is 87%,[17] NTT for the primary outcome would be 2.4 (1.9-3.4). Other outcomes did not differ significantly between lithium and placebo. One study[9] reported that there were no significant differences in discontinuation due to adverse events, death, or death by suicide between the groups.

3.3 | Lamotrigine vs placebo

Lamotrigine was also found to be superior to placebo for reducing the relapse rate due to any mood episode [RR = 0.81, 95%CI = 0.70-0.93, $P = 0.004$, $I^2 = 0\%$, NNT = 8.3 (5.0-25.0)] and for all-cause discontinuation [RR = 0.89, 95% CI = 0.81-0.98, $P = 0.02$, $I^2 = 52\%$, NNT = 11.1 (7.1-25.0)], as detailed in Figure S4. If the CER was 87%,[17] NTT for the primary outcome would be 6.0 (3.8-16.4). Other outcomes did not differ significantly between lamotrigine and placebo.

4 | DISCUSSION

These results suggest that lithium and lamotrigine are beneficial for preventing relapse in clinically stable patients with adult BD. Although we did not directly compare lithium with lamotrigine regarding relapse rate, lithium appeared to be associated with a lower risk in this regard compared to lamotrigine. Both drugs were well tolerated. However, the number of studies and patients included in this analysis was small. There was also a difference in duration of the studies between the two lithium investigations. Future investigations should examine longer-term efficacy and generate more safety data. We did not evaluate several efficacy and safety outcomes for lithium because no suitable data were available for performing these meta-analyses. We importantly note that all the DBRPCTs included in the analysis were industry sponsored; therefore, the results might reflect an industry-sponsored bias.[16]

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CONFLICT OF INTEREST

The authors have declared that there are no conflicts of interest in relation to the subject of this study. We have had the following interests within the past 3 years. Dr. Oya has received speaker's honoraria from Chugai, Dainippon Sumitomo, Eisai, Eli Lilly, Janssen, Kissei, Meiji, MSD, Otsuka, and Tanabe-Mitsubishi and has received research grants from Fujita Health University School of Medicine. Dr. Sakuma has received speaker's honoraria from Meiji, Otsuka, and Torii. Dr. Esumi has no conflict of interest relationship with any company. Dr. Hashimoto has no conflict of interest relationship with any company. Mr. Hatano has received speaker's honoraria from Otsuka. Dr. Matsuda has received speaker's honoraria from Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Tanabe-Mitsubishi and has received a grant-in-aid for Young Scientists (B). Dr. Matsui has received speaker's honoraria from Dainippon Sumitomo, Janssen, and Meiji. Dr. Miyake has received speaker's honoraria from Dainippon Sumitomo, Eisai, Meiji, Otsuka, and Tanabe-Mitsubishi. Dr. Nomura has received speaker's honoraria from Meiji, MSD, Janssen, Otsuka, and Torii. Dr. Okuya has received speaker's honoraria from Meiji and Torii. Dr. Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Novartis, Otsuka, Pfizer, Shionogi, and Yoshitomi and research grants from GlaxoSmithKline and Otsuka. Dr. Kato has received grant funding from Japan Society for the Promotion of Science, SENSHIN Medical Research Foundation and Japan Research Foundation for Clinical Pharmacology, and speaker's honoraria from Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, MSD, Ono, Otsuka, Pfizer, Shionogi, Takeda, and Tanabe-Mitsubishi. Dr. Hashimoto has received speaker's honoraria from Dainippon Sumitomo, Mnochida, Novartis, Takeda, Meiji Seika, Shionogi, Eli Lilly, and Astellas Dr. Mishima has received research support from the Japanese Ministry of Health, Labor and Welfare, the Japanese Ministry of Education, Science, and Technology, and the National Center of Neurology and Psychiatry Intramural Research Grant for Neurological and Psychiatric Disorders and speaker's honoraria from Eisai, Takeda, Astellas, and Janssen along with research grants from Eisai, Nobelpharma, and Takeda. Dr. Watanabe has received research funds from the Japanese Ministry of Health Labor and Welfare, and the Japanese Ministry of Education, Science, and Technology and also received royalties from Sogensha and Akatsuki. Dr. Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, Janssen, Otsuka, Meiji, MSD, Tanabe-Mitsubishi, and Yoshitomi and has received a Health Labor Sciences Research Grant and a Fujita Health University School of Medicine research grant.

ETHICAL STATEMENTS

This material has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in another journal. All authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

DATA REPOSITORY

I agree to deposit the data and publish whole of it as supplemental information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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