Cochrane Database of Systematic Reviews | Review - Intervention

Lamotrigine in the maintenance treatment of bipolar disorder

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Authors' declarations of interest

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Abstract

Background

Bipolar disorder is a chronic mental disorder with repetitive mania/hypomania as well as depressive episodes, which eventually results in marked impairment in overall functioning and health-related quality of life. A worldwide prevalence rate of 2.4% has been reported. The risk of suicide is higher in people with bipolar disorder than those with other mental disorders. Therefore, effective management of bipolar disorder in the maintenance period is warranted to minimize the risk of relapse or recurrence. Although lithium has been the standard treatment of bipolar disorder for many years, it is associated with adverse effects and teratogenicity. Lamotrigine is approved to be expected for prevention of recurrence for the maintenance treatment of bipolar disorder. In addition, lamotrigine is as effective as lithium. Therefore, we performed a systematic review to confirm the efficacy and safety of lamotrigine in the maintenance treatment of bipolar disorder.

Objectives

To assess the efficacy and tolerability of lamotrigine in the maintenance treatment of bipolar disorder.

Search methods

We searched Ovid MEDLINE, Embase, PsycINFO, the Cochrane Common Mental Disorders Group's Specialized Register (CCMDCTR) and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 21 May 2021. We also searched international trial registries and contacted experts in the field.

Selection criteria

We included randomized controlled trials enrolling adults with bipolar disorder who were treated with lamotrigine, placebo or lithium.

Data collection and analysis

Two reviews authors independently checked the eligibility of studies and extracted data using a standardized form. Data extracted included study characteristics, participant characteristics, intervention details, settings, and outcome measures in the term of efficacy and tolerability. Study information were then entered into RevMan web.

Main results

We included 11 studies with a total of 2314 participants in this review; 1146 were randomized to lamotrigine, 869 were randomized to placebo and, 299 to lithium.

We rated all studies as having an unclear risk of bias in at least one domain of Cochrane's tool for assessing risk of bias, with the most commonly observed weakness being selection bias (random sequence generation and allocation concealment). We judged five studies to be at a high risk of detection bias (blinding of outcome assessment). These potential biases pose as major threat to the validity of the included studies in this review.

Outcomes of efficacy showed a possible advantage of lamotrigine over placebo. The estimated risk ratio (RR) for recurrence of manic symptom at one year as measured by the Young Mania Rating Scale (YMRS) was 0.67, (95% confidence interval (CI) 0.51 to 0.87; 3 studies, 663 participants; low-certainty evidence) in favor of lamotrigine. The RR of clinical worsening with the need for additional psychotropic treatment (RR 0.82, 95% CI 0.70 to 0.98; 4 studies, 756 participants) based on moderate-certainty evidence. The possible benefits of lamotrigine were also seen for the outcome of treatment withdrawal due to any reason at 6-12 months after treatment (RR 0.88, 95% CI 0.78 to 0.99; 4 studies, 700 participants; moderate-certainty evidence). Regarding tolerability, our analyses showed that the incidence rates of adverse effects were similar between the lamotrigine group and the placebo group (short-term effect: RR 1.07, 95% CI 0.81 to 1.42; 5 studies, 1138 participants; very low-certainty evidence; long-term effect: RR 0.97, 95% CI 0.77 to 1.23; 4 studies, 756 participants; moderate-certainty evidence).

In the comparison between lamotrigine and lithium, efficacy was similar between groups except for recurrence of mania episode at one year. Recurrence of manic symptoms was higher in the lamotrigine group than that of the lithium group (RR 2.13, 95% CI 1.32 to 3.44; 3 studies, 602 participants; moderate-certainty evidence). Analysis of adverse effects at 6-12 months showed that a lower proportion of participants experienced at least one adverse effect when treated with lamotrigine compared to lithium (RR 0.70, 95% CI 0.51 to 0.96; 4 studies, 691 participants; moderate-certainty evidence).

Authors' conclusions

Low- to moderate-certainty evidence collectively suggests that lamotrigine may be superior to placebo as a treatment modality for bipolar disorder. In comparison to lithium, people with bipolar disorder seem to tolerate lamotrigine better in the long run; however, the demonstrated efficacy in the maintenance of bipolar disorder was similar between the two groups.

Plain language summary

Available in **English** | Español | Français | 日本語 | Bahasa Malaysia | Polski | 简体中文

Lamotrigine as a treatment for prevention of recurrence of bipolar disorder

Review question

To investigate the clinical effectiveness (benefits and harms) of lamotrigine for maintenance therapy of bipolar disorder in comparison with placebo, combination therapy or existing drugs (e.g. lithium, olanzapine).

Background

Lamotrigine is approved for the maintenance treatment (treatment for prevention of recurrence) of bipolar disorder. It could be a viable and effective treatment strategy for the maintenance of bipolar disorder, where it demonstrated a lower risk of recurrence than placebo. In addition, it has been reported to be as effective as lithium. Therefore, we performed a systematic review to investigate the efficacy and safety of lamotrigine in the maintenance treatment (treatment for prevention of recurrence) of bipolar disorder.

Key findings

The evidence is current to May 2021. We included 11 studies in this review with a total 2314 participants. 1146 participants were assigned to lamotrigine, and 1168 participants were assigned to control intervention (869 received placebo and 299 received lithium).

Our review identified the following.

Lamotrigine versus placebo

Benefits: lamotrigine was found to be superior over placebo in the following outcomes.

1) Reduced the rate of recurrence of manic symptoms

2) Suppressed depressive symptoms

3) Less need for additional therapeutic agents for the recurrence of all symptoms

4) Reduction in the withdrawal rate due to any causes six months or more after the initiating of intervention

Harms: adverse-event profile of lamotrigine was similar to that of placebo.

Lamotrigine versus lithium

Benefits: lamotrigine was as effective as lithium, except for the recurrence of manic symptoms, for which the rate was higher in people who received lamotrigine than people treated with lithium.

Harms: the rate of adverse events associated with lamotrigine was lower than that of lithium.

Certainty of the evidence

We assessed the certainty of our included evidence to be very low to moderate. This is because majority of the included trials did not describe how treatment allocation was concealed. Given that we were unable to identify high-confidence evidence the overall findings of this systematic review should be interpreted carefully.

Conclusions

Lamotrigine may be superior to placebo in efficacy and may be comparable in safety. And then, lamotrigine was as effective as lithium except for its recurrence rate of mania, and was superior to lithium in terms of safety. Future studies in this field with robust methods and transparent reporting are needed to confirm our results and to fully answer our

pre-specified review question.

Authors' conclusions

Implications for practice

Findings from our review showed a potential superiority of lamotrigine over placebo in terms of recurrence prevention and treatment continuation. The incidence of adverse effects was similar between lamotrigine and placebo regardless of the duration of the studies. Therefore, lamotrigine is considered to be sufficiently useful in the maintenance treatment for bipolar disorder. In comparison with lithium, change in rating scale mania as well as depression, addition of therapeutic intervention for any mood episodes, treatment continuation, and recurrence of depressive episode for one year were similar in lamotrigine. Although lamotrigine worsened the recurrence of mania episode for one year, tolerability was superior to lamotrigine for lithium. These results are consistent with current guidelines for treatment of bipolar disorder (Yatham 2018). In the pharmacotherapy of bipolar disorder, the use of antipsychotic agents as well as mood stabilizers has been increased in recent years. However, these are primarily treatments for manic symptoms of bipolar disorder; there is no robust treatment strategy for depressive symptoms during the maintenance phase. Lithium, which has been used as standard first-line treatment, is associated with severe adverse effects and thus prone to treatment discontinuation and non-compliance. Furthermore, in Japan, lithium is contraindicated for pregnant and lactating women. In this review, we could not comprehensively evaluate the safety profile of lamotrigine for pregnant and lactating women due to insufficient data. Nonetheless, our findings on relapse prevention by lamotrigine suggests that it is a viable maintenance treatment option for people with bipolar disorder.

Implications for research

The overall low- to moderate-certainty evidence is indicative of the need to design and execute robust, large-scale randomized studies of lamotrigine amongst people with bipolar disorder, with particular considerations on the methodological shortcomings in randomization method, allocation concealment and blinding of outcome assessment as identified in our review. For effective clinical decision-making, results of our present review will contribute to an ongoing network meta-analysis of drug treatments for people with bipolar disorder, which aims to provide a solid evidence base in regards to efficacy and safety of the wide array of drug treatment options available for bipolar disorder.

We initially planned to explore the efficacy and safety profile of lamotrigine (as monotherapy or in combination with other pharmacological agents) in pregnant and lactating women, and assessing the quality of life or satisfaction amongst treated individuals. However, we did not identify eligible studies involving pregnant and lactating women and none of the studies assessed quality of life or patient satisfaction. These are important knowledge gaps and their evidence is critical for effective clinical practice management, in particular to enhance treatment safety and compliance. We urge study investigators in the field to continue, and should be systematically reviewed.

Summary of findings

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Summary of findings 1. Lamotrigine versus placebo for the maintenance treatment of bipolar disorder

Lamotrigine versus placebo in the maintenance treatment of bipolar disorder

Patient or population: bipolar disorder
Setting: hospital outpatients
Intervention: lamotrigine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with lamotrigine				
Recurrence of any episodes at one year (hospitalization for any episodes)	Study population		-	(0 studies)	-	The outcome was not reported in any studies.
	see comment	see comment				
Recurrence of any episodes at one year (Young Mania Rating Scale (YMRS) total score ≥15 for manic episode)	Study population		RR 0.67 (0.51 to 0.87)	663 (3 RCTs)	⊕⊕⊖⊖ LOW [1 2 3]	2 studies reported that no recurrence of any episodes for one year Young Mania Rating Scale total score 15 or greater for manic episode was recorded in the lamotrigine and control groups.
	217 per 1,000	87 per 1,000 (48 to 159)				
Recurrence of any episodes at one year (Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥15	Study population		RR 0.85 (0.70 to 1.02)	1606 (7 RCTs)	⊕⊕⊖⊖ LOW [1 4 5]	

for depressive episode; Hamilton Depression Rating Scale (HDRS) total score ≥14 for depressive episode)	516 per 1,000	438 per 1,000 (340 to 536)			
Recurrence of any episodes at one year for clinical worsening with additional psychotropics (mood stabilizers, antidepressants, antipsychotics or benzodiazepines)	Study population		RR 0.82 (0.70 to 0.98)	756 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1 6]
	595 per 1,000	500 per 1,000 (428 to 577)			
Recurrence of any episodes at one year (active suicidal behavior)	Study population		not estimable	(1 study)	- The outcome was measured in one study, but no numeric data were provided.
	0 per 1,000	0 per 1,000 (0 to 0)			
Withdrawal from treatment due to any reason, up to 12 weeks after intervention commencement (short term)	Study population		RR 1.10 (0.70 to 1.74)	195 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 7 8]
	288 per 1,000	317 per 1,000 (196 to 472)			
Withdrawal from treatment due to any reason, 6-12 months after intervention initiation (long term)	Study population		RR 0.88 (0.78 to 0.99)	700 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1 6]
	686 per 1,000	529 per 1,000 (426 to 625)			
Any reported adverse effects up to 12 weeks after starting treatment (short term)	Study population		RR 1.07 (0.81 to 1.42)	1138 (5 RCTs)	⊕⊖⊖⊖ VERY LOW [1 9 10]
	239 per 1,000	256 per 1,000 (208 to 311)			
Any reported adverse effects 6-12 months after initiating the intervention (long term)	Study population		RR 0.97 (0.77 to 1.23)	756 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1 6]
	536 per 1,000	514 per 1,000 (428 to 594)			
Recurrence of manic episode at one year	Study population		RR 0.91 (0.66 to 1.26)	574 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1 11]
	229 per 1,000	211 per 1,000 (149 to 288)			
Recurrence of depressive episode at	Study population		RR 0.75	574	⊕⊕⊕⊖

one year	382 per 1,000	294 per 1,000 (225 to 374)	(0.53 to 1.05)	(3 RCTs)	MODERATE [1 11]	
Quality of life as measured by the 36-Item Short Form Health Survey	-	see comment	-	(0 study)	-	The outcome was not reported in any studies.
Total severity score from depression and mania symptom scores, such as HDRS and the YMRS	-	MD 0 (0 to 0)	-	(0 study)	-	The outcome was not reported in any studies.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Publication bias was not evaluated due to limited data.

[2] Downgraded by one level for risk of bias. Calabrese 1999, Calabrese 2000 and Calabrese 2003 had unclear to high risk of detection bias (blinding of outcome assessment).

[3] Downgraded by one level. Only Calabrese 2000 provided OR and 95% CI.

[4] Downgraded by one level for inconsistency (I^2= 60%).

[5] Downgraded by one level for risk of bias. Calabrese 1999, Calabrese 2000, Calabrese 2003 and Calabrese 2008 had unclear to high risk of detection bias (blinding of outcome assessors).

[6] Downgraded by one level for risk of bias. Bowden 2003, Calabrese 2000, Calabrese 2003 and Koyama 2011 had unclear to high risk of detection bias (blinding of outcome assessment).

[7] Downgraded by one level for risk of bias (only Calabrese 1999 was included with unclear risk of bias).

[8] Downgraded by one level. Only Calabrese 1999 provided OR and 95% CI.

[9] Downgraded by one level for risk of bias. Calabrese 1999 and Calabrese 2008 had unclear to high risk of detection bias (blinding of outcome assessment).

[10] Downgraded by two levels for very serious inconsistency (I^2= 82%)

[11] Downgraded by one level for risk of bias. Bowden 2003, Calabrese 2003 and Koyama 2011 had unclear to high risk of detection bias (blinding of outcome assessment).

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Summary of findings 2. Lamotrigine versus lithium for the maintenance treatment of bipolar disorder

Lamotrigine versus lithium in the maintenance treatment of bipolar disorder

Patient or population: bipolar disorder
Setting: hospital outpatients
Intervention: lamotrigine
Comparison: lithium

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lithium	Risk with lamotrigine				
Recurrence of any episodes at one year (hospitalization for any episodes)	Study population		-	(0 studies)	-	The outcome was not reported in any studies.
	see comment	see comment				
Recurrence of any episodes at one year (Young Mania Rating Scale (YMRS) total score ≥15 for manic episode)	Study population		RR 3.57 (0.15 to 85.39)	376 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 3]	

	0 per 1,000	0 per 1,000 (0 to 0)				
Recurrence of any episodes at one year (Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥15 for depressive episode; Hamilton Depression Rating Scale (HDRS) total score ≥14 for depressive episode)	Study population		RR 1.40 (0.70 to 2.79)	376 (2 RCTs)	⊕⊕⊖⊖ LOW [1 3 4]	
	65 per 1,000	92 per 1,000 (44 to 179)				
Recurrence of any episodes at one year for clinical worsening with additional psychotropics (mood stabilizers, antidepressants, antipsychotics or benzodiazepines)	Study population		RR 1.11 (0.92 to 1.35)	602 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3 5]	
	408 per 1,000	461 per 1,000 (380 to 543)				
Recurrence of any episodes at one year (active suicidal behavior)	Study population		RR 1.01 (0.06 to 15.91)	155 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 3 6]	
	13 per 1,000	13 per 1,000 (1 to 176)				
Withdrawal from treatment due to any reason, up to 12 weeks after intervention commencement (short term)	Study population		-	(0 studies)	-	The outcome was not reported in any studies.
	see comment	see comment				
Withdrawal from treatment due to any reason, 6-12 months after intervention initiation (long term)	Study population		RR 0.96 (0.88 to 1.05)	636 (4 RCTs)	⊕⊕⊕⊖ MODERATE [3 7]	
	663 per 1,000	590 per 1,000 (491 to 677)				
Any reported adverse effects up to 12 weeks after starting treatment (short term)	Study population		-	(0 studies)	-	The outcome was not reported in any studies.
	see comment	see comment				
Any reported adverse effects 6-12 months after initiating the intervention (long term)	Study population		RR 0.70 (0.51 to 0.96)	691 (4 RCTs)	⊕⊕⊕⊖ MODERATE [3 7]	
	382 per 1,000	226 per 1,000 (164 to 294)				
Recurrence of manic episode at one year	Study population		RR 2.13 (1.32 to 3.44)	602 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3 7]	

	102 per 1,000	206 per 1,000 (136 to 298)				
Recurrence of depressive episode at one year	Study population		RR 0.83 (0.63 to 1.09)	602 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3] [7]	
	355 per 1,000	295 per 1,000 (227 to 373)				
Quality of life as measured by the 36-Item Short Form Health Survey	-	see comment	-	(0 studies)	-	The outcome was not reported in any studies.
Total severity score from depression and mania symptom scores, such as HDRS and the YMRS	-	see comment	-	(0 studies)	-	The outcome was not reported in any studies.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded by one level for risk of bias (only Suppes 2008a was included).

[2] Downgraded by two levels due to wide CIs.

[3] Publication bias was not evaluated due to limited data.

[4] Downgraded by one level due to wide CIs.

[5] Downgraded by one level for risk of bias. Bowden 2003 and Calabrese 2003 were judged to be at high risk of detection bias (blinding of outcome assessment).

[6] Downgraded by one level for risk of bias (only Licht 2010 was included).

[7] Downgraded by one level for risk of bias. Calabrese 2003 and Licht 2010 were judged to be at high risk of detection bias (blinding of outcome assessment).

Background

Description of the condition

Bipolar disorder is a chronic mental disorder with repetitive cycles of mania/hypomania as well as depressive episodes, which eventually results in marked impairment in overall functioning and health-related quality of life (de Hert 2011). It is described by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) tool as a type of mental health condition that leads to extreme fluctuation in a person's mood, energy, and ability to function (American Psychiatric Association 2013). Bipolar disorder was the 46th greatest causes of disability-adjusted life years (DALYs) in the world, placing it ahead of Alzheimer's disease and other dementias among the 291 disorders included in the Global Burden of Disease Study 2010 (Murray 2012), and it has a worldwide prevalence of 2.4% (Merikangas 2011). Bipolar disorder affects approximately 60 million people worldwide (WHO 2019a). The risk of suicide is higher in people with bipolar disorder than those with other mental disorders (Nordentoft 2011). The estimated rate of death by suicide was 0.2 people per year to 0.4 people per year among people with bipolar disorder (Sondergard 2008), and one-year recurrence rate was 26.3% (Vazquez 2015). Therefore, in addition to treating recurrent mania/hypomania and depressive episodes, effective management of bipolar disorder after acute treatment of mood episodes using long-term continuation therapy is warranted in order to minimize the risk of relapse or recurrence (Calabrese 2006).

Description of the intervention

For many years, lithium has been the standard treatment of bipolar disorder with acute mood episodes, polarity change prevention, prophylactic treatment, and suicide prevention (BALANCE investigators and collaborators 2010; Smith 2007; Yildiz 2011). However, questions were raised over the potential overestimation of the effectiveness of lithium and the frequency of use of lithium for bipolar disorder is decreasing (Blanco 2002; Lyall 2019). Furthermore, lithium has been associated with congenital malformations during pregnancy for the fetus (Poels 2018). It has been reported that rates of recurrence after lithium discontinuation sharply increased postpartum (Viguera 2000). Sodium valproate and carbamazepine, both antiepileptic drugs, are effective for the management of the bipolar mania and acute symptoms (Bowden 2005; Greil 1998); however, they are relatively less effective against depression of maintenance phase and depression of bipolar disorder (Ng 2007). Atypical antipsychotics including olanzapine (Berk 1999b), quetiapine (Calabrese 2005; Ketter 2007), aripiprazole (Keck 2003), and risperidone (Segal 1998) have also demonstrated efficacy in the treatment of mania. For the new anticonvulsants such as gabapentin (Vieta 2006), topiramate (Pigott 2016), zonisamide (Dauphinais 2011), and levetiracetam (Kaufman 2004), sufficient efficacy has not been demonstrated for bipolar disorder. Thus, there remains a need to identify additional pharmacological agents with sufficient and up-to-date evidence to demonstrate their effectiveness in preventing and managing relapse of bipolar disorder.

Lamotrigine is approved for the maintenance treatment of adults with bipolar disorder. Lamotrigine is indicated for use in numerous clinical guidelines as a first-line pharmacological agent in the treatment of bipolar depression (Nivoli 2011). Lamotrigine is licensed by the US Food and Drug Administration (FDA) for the prevention of relapses in people with bipolar disorder. Although the evidence base regarding long-term efficacy of lamotrigine is reasonably robust, five pivotal trials conducted in acute-phase therapy reported relatively neutral findings and they found no statistically significant benefits (Calabrese 2008). Previous studies found that lamotrigine could be a viable and effective treatment modality for the maintenance of bipolar disorder, where it illustrated a lower risk of recurrence than placebo (Geddes 2009; Miura 2014; Oya 2019). It has also been reported to be equally effective as lithium, which is the standard treatment for bipolar disorder (Suppes 2008b). In addition, lamotrigine demonstrated a better safety profile compared to lithium in postpartum teratogenicity (Graham 2018), although available evidence from a population-based cohort study found that

it was equivalent to lithium in the prevention of (hypo) manic or depressive episodes (Wesseloo 2017). It is worth highlighting that lamotrigine has been proposed as a treatment option for bipolar disorder during pregnancy among mothers who are at risk of depression. For example, Kong 2018 indicated that lamotrigine could be a safe mood stabilizer for use during pregnancy based on available clinical evidence; Veroniki 2017 conducted a systematic review on the safety of antiepileptic drugs in pregnancy which included 96 (n=58,461 patients) studies, most were cohort studies. The risk of congenital malformations with lamotrigine was comparable to placebo (OR, 0.96; 95% CI, 0.72–1.25). and less than with other antiepileptic drugs (ethosuximide (OR, 3.04; 95% CI, 1.23–7.07), valproate (OR, 2.93; 95% CI, 2.36–3.69), topiramate (OR, 1.90; 95% CI, 1.17–2.97), phenobarbital (OR, 1.83; 95% CI, 1.35–2.47), phenytoin (OR, 1.67; 95% CI, 1.30–2.17), carbamazepine (OR, 1.37; 95% CI, 1.10–1.71).

How the intervention might work

Lamotrigine is an antiepileptic drug belonging to the phenyltriazine class used in the treatment of epilepsy and bipolar disorder. Lamotrigine works by inhibiting voltage-sensitive sodium channels, stabilizing presynaptic neuronal membranes and inhibiting glutamate release (Verrotti 2018). The proposed mechanisms of action to explain the treatment of lamotrigine for bipolar disorder include inhibiting voltage-sensitive sodium channels, glutamate release and calcium channel blockade (Andreazza 2014). To reduce the risk of life-threatening skin rashes, lamotrigine needs to be titrated slowly. Thus, lamotrigine is more effective as maintenance therapy than in the acute treatment of bipolar disorder (Bobo 2017; Calabrese 2008). Although the effects of lamotrigine on pregnancy have been reported in a previous systematic review, there was no association with birth defects or related disorders (Pariente 2017). Lamotrigine has been shown to demonstrate more predictable pharmacokinetics than other antiepileptic drugs such as carbamazepine and valproic acid or valproate, which have a pronounced interindividual variability in their pharmacokinetics and a narrow therapeutic range (Johannessen 2006). As with other antiepileptic drugs, there are demonstrable effects of metabolic enzymes but oral bioavailability is almost 100%, with negligible influence from diets (Garnett 1997). Consequently, treatment of lamotrigine is associated with less burden in blood sampling/therapeutic monitoring inflicted on people with bipolar disorder.

Why it is important to do this review

Reviews exploring the effectiveness of lamotrigine are available (Bowden 2012b; Yatham 2018). However, these existing reviews considered non-maintenance therapies as part of their scope, and the numbers of included studies and study participants were small. Consequently, we planned to conduct this Cochrane Review to synthesize the latest available evidence in order to provide a comprehensive update on the effectiveness of lamotrigine for maintenance treatment of bipolar disorder. Although lithium is used as the first-line drug for the treatment of bipolar disorder, results from randomized studies on the comparative efficacy of lamotrigine versus lithium are inconsistent and thus we hoped to review and synthesize evidence using rigorous and systematic methods. We examined the effectiveness of lamotrigine against placebo as well as combination therapy and existing medications.

Objectives

To determine efficacy and safety of lamotrigine for the maintenance treatment of manic, depressive, and mixed episodes of bipolar disorder.

Methods

Criteria for considering studies for this review

Types of studies

We included individually-randomized controlled trials. Cluster-randomized trials were eligible for inclusion but none were identified. If studies employing a cross-over design had been identified and included, we would only have used only data from the first active treatment (i.e. first randomized phase before crossing over). Studies published as full texts or only as abstracts as well as unpublished data were eligible for inclusion.

Types of participants

We included people with bipolar I or II disorder in remission, with a diagnosis based on the International Classification of Diseases 11th Revision (ICD-11) coding system (WHO 2019b), or the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) tool (or previous versions of these diagnostic manuals) (American Psychiatric Association 2013). Study participants were aged 18 years or older of either gender with concurrent primary diagnosis of Axis I or Axis II disorder. We included participants with any co-morbidities except for those with dementia and personality disorder or cyclothymia, which was defined as a disorder not meeting the requirements to be classified as a major episode of hypomanic and depressive state.

Types of interventions

We included studies comparing lamotrigine with usual care, placebo or no treatment; the daily dosage of lamotrigine maintenance treatment was defined to range from 100 mg to 500 mg with a treatment duration of more than 12 weeks.

We were interested in the following treatment comparisons:

- lamotrigine versus no treatment;
- lamotrigine versus placebo;
- lamotrigine versus lithium;
- lamotrigine versus valproic acid or valproate (or both);
- lamotrigine versus olanzapine;
- lamotrigine versus quetiapine;
- lamotrigine plus lithium versus lithium;
- lamotrigine plus lithium versus lamotrigine;
- lamotrigine plus valproic acid or valproate (or both) versus valproic acid or valproate (or both);
- lamotrigine plus valproic acid or valproate (or both) versus lamotrigine;
- lamotrigine plus olanzapine versus olanzapine;
- lamotrigine plus olanzapine versus lamotrigine;
- lamotrigine plus quetiapine versus quetiapine;

- lamotrigine plus quetiapine versus lamotrigine.

Types of outcome measures

Timing of outcome assessment

We anticipated that authors of studies would report response rates at various time points during and post-intervention. Therefore, we subdivided the timing of outcome assessment as follows:

- short-term effects, within 12 weeks after treatment initiation;
- long-term effects, at 6 to 12 months after treatment initiation.

Hierarchy of outcome measures

If several measures were available for each outcome, we used results from the Hamilton Depression Rating Scale (HDRS). If HDRS results were not available, we used results from the Montgomery-Asberg Depression Rating Scale (MADRS) for depressive episode as the primary outcome. However, if outcomes were measured by other rating scales, we included and extracted these results with explanations on the components of the scale used by the respective included studies.

Primary outcomes

Our primary outcome measures of interests were as follows.

- Recurrence of any episode at one year:
  - hospitalization for any mood episodes;
  - Young Mania Rating Scale (YMRS) total score ≥15 for manic episode (Young 1978);
  - Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 15 for depressive episode (Montgomery 1979); Hamilton Depression Rating Scale (HDRS) total score ≥ 14 for depressive episode (Hamilton 1960);
  - clinical worsening with the need for additional treatment (e.g. mood stabilizers, antidepressants, antipsychotics or benzodiazepines);
  - active suicidal behavior.
- Withdrawal from treatment due to any reason:
  - short term, up to 12 weeks after treatment initiation (range: 7 to 16 weeks);
  - long term, at least six months after treatment initiation (range: 6 to 16 months).
- Adverse effects:
  - short term, up to 12 weeks after treatment initiation (range: 7 to 16 weeks);
  - long term, at 6 to 12 months after treatment initiation (range: 6 to 16 months).

Secondary outcomes

We included the following secondary outcome measures:

- recurrence of manic episode at one year (based on assessor's judgement without using an evaluation scale);
- recurrence of depressive episode at one year (based on assessor's judgement without using an evaluation scale) ;

- quality of life as measured by the mental component summary of the 36-Item Short Form Health Survey (SF-36) (Ware 1993);
- total severity score calculated from adding depression and manic symptom scores, such as the HDRS and the YMRS (Hamilton 1960; Young 1978).

For timing of outcome assessment, we anticipated that authors of studies would report response rates at various time points during and post-intervention. Therefore, we subdivided the timing of outcome assessment as follows:

- short term effects, up to 12 weeks after treatment initiation (range: 7 to 16 weeks);
- long term effects, at least six months after treatment initiation (range: 6 to 16 months).

If several measures were available for each outcome, we used results from the HDRS. If HDRS results were unavailable, we used results from MADRS. However, if outcomes were measured by other rating scales not listed above, we included and extracted the relevant results with explanations on the components of the scale used by the respective included studies.

Search methods for identification of studies

Electronic searches

An information specialist from the Cochrane Common Mental Disorders Group searched the following databases on 21 May 2021 using relevant keywords, subject headings (controlled vocabularies) and search syntax, appropriate to each resource (Appendix 1):

- Cochrane Central Register of Controlled Trials (CENTRAL), (Issue 5 of 12, 2021) on the Cochrane Library;
- Cochrane Database of Systematic Reviews (CDSR) (Issue 5 of 12, 2021) on the Cochrane Library;
- Ovid MEDLINE (1946 to May 21, 2021);
- Ovid Embase (1974 to 2021 Week 21);
- Ovid PsycINFO (to May Week 3 2021).
- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all years to June 2016) (Appendix 2).

We searched ClinicalTrials.gov (clinicaltrials.gov/), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), to identify unpublished or ongoing studies.

We did not impose any restrictions on date, language or publication status to the searches.

Searching other resources

We screened reference lists of relevant narrative reviews and included studies for further relevant information. For information on unpublished data or ongoing studies, we attempted to contact the study investigators or content experts in the field (or both) in an attempt to identify additional trial data.

Data collection and analysis

Selection of studies

Two review authors (YH and KK) independently screened titles and abstracts from the systematic literature search and excluded clearly irrelevant records. For any disagreements, we consulted other review authors (TF or SS, or both). We identified and excluded duplicates and collated multiple reports of the same study so that each study, not each reference, was the unit of interest in the review.

We retrieved full-text versions of all 'to include' or 'unclear' records for further assessment against our pre-defined eligibility criteria. We attempted to obtain translations of articles that were published in languages other than English or Japanese. For conference abstracts, we attempted to retrieve relevant subsequent full-text publication or contacted the study investigators for clarification. Two review authors (YH and KK) independently screened the full texts against the pre-specified inclusion/exclusion criteria. We resolved disagreements by discussion or by consulting other review authors (TF or SS, or both)

Data extraction and management

Two review authors (YH and KK) independently extracted the following information from included studies using a pre-standardized data collection form.

- Methods: study design, total duration of study, methods of randomization, methods of allocation concealment, withdrawals.
- Participants: number, mean age, age range, gender, inclusion and exclusion criteria, diagnosis (bipolar disorder I type or type II), baseline comparability between two groups, severity of condition, mean scores on HDRS, or MADRS, or any other episode scale at baseline and end of studies, time from onset and losses to follow-up.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcome data and characteristics.
- Others: setting, publication year, sources of funding, intention-to-treat (ITT) analysis.

We resolved any disagreements regarding the extracted study information by discussion or by consulting other review authors (TF or SS, or both).

Assessment of risk of bias in included studies

Two review authors (YH and KK) independently assessed risk of bias in included studies using Cochrane's tool for assessing risk of bias as indicated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We resolved disagreements by discussion or by consulting other review authors (TF or SS, or both).

We assessed risk of bias in included studies according to the following seven domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We judged each potential source of bias as 'high risk', 'low risk' or 'unclear risk', and provided a supporting quotation from the study report together with a justification for our judgements in the risk of bias table. We summarized our judgements across different studies for each domain.

Measures of treatment effect

If the included studies reported continuous data such as total severity scores using the same measurement scale, we planned to synthesize the effect measures using mean differences (MDs) with 95% confidence intervals (CIs); had studies used different measurement tools, we planned to calculate the standardized mean differences (SMDs). For dichotomous data such as the number of reported adverse effects, we calculated the risk ratios (RRs) with 95% CIs.

Unit of analysis issues

Cross-over studies

One concern of cross-over trials is the carry-over effect, where the anticipated and unprecedented pharmacological, physiological and psychological effects of the study treatment intervention in the first phase may affect the results of the second phase of the study. As a result, in the second phase, participants can differ systematically from their initial state, even after a washout period.

For the purpose of this Cochrane Review, had we included cross-over studies, we would have considered only results from the first phase, i.e. prior to crossing over.

Cluster-randomized trials

For cluster-randomized trials, we planned to make an adjustment to the sample size for each intervention based on the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), using an estimate of the intraclass correlation coefficient (ICC) derived from the study (where available) or from a similar study or from a study of a similar population. We intended to conduct a sensitivity analysis to explore the effects of variation in ICCs and the overall robustness of our findings (Sensitivity analysis). Impact of studies for which no ICC was reported on the overall review findings would have been explored in a sensitivity analysis (Sensitivity analysis).

Studies with multiple treatment groups

Where a relevant study involved more than two treatments groups, we included data from the additional arms for comparisons. If the data were binary, we combined them in a 2 × 2 table. If data were continuous, we combined them using the formula provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Dealing with missing data

We recorded missing data for each included study and attempted to contact the study investigators for the missing information. Where possible, we performed all meta-analyses using an intention-to-treat (ITT) approach i.e. we analyzed all participants and their outcomes within the groups to which they were originally allocated, regardless of whether they received the intervention.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting the calculated effect estimates and CIs in the forest plots. We used the Chi^2 test (statistical significance at $P < 0.1$) and the I^2 statistic to investigate and quantify statistical heterogeneity in each meta-analysis. We interpreted the I^2 statistic as follows (Higgins 2020):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

Assessment of reporting biases

Reporting biases arise when dissemination of research findings is often influenced by the nature and direction of the results (Higgins 2020). We planned to conduct a funnel plot to investigate publication bias through visual inspection of asymmetry should sufficient evidence be available (10 or more included studies) for each outcome, also planned to perform a statistical test for funnel plot asymmetry as proposed by Egger and Rücker (Egger 1997; Rücker 2008).

Data synthesis

One review author (KK) entered data into the RevMan web, and a second review author (YH) checked the entries. Due to variations in participants, interventions or outcomes, we used a random-effects meta-analysis to produce an overall summary.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following four subgroup analyses for our Primary outcomes should data be sufficient:

- with or without mental disorder co-morbidities;
- duration of treatment (up to six months and longer than six months);
- setting (community versus hospital);
- for each pharmacological modality such as mood stabilizer, antipsychotic and antidepressant.

Sensitivity analysis

We planned to conduct a sensitivity analysis to examine the impact of the ICCs (Unit of analysis issues) mentioned above.

In addition, sensitivity analyses were also planned under the following conditions to determine if the risk area of bias would affect the overall robustness of the findings:

- excluding studies with inadequate allocation concealment and random sequence generation;
- excluding studies in which outcome evaluation was not blinded;
- excluding studies in which loss to follow-up was not reported or was greater than 10%;
- excluding studies funded by the pharmaceutical company marketing lamotrigine.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table based on the GRADE assessment system using the GRADEpro GDT software for each of the main comparisons, considering the two most clinically important primary outcomes (Guyatt 2011). Two review authors (YH and KK) independently graded the body of evidence using adapted decision rules. We explored the following five domains:

1. risk of bias;
2. inconsistency;
3. indirectness;
4. imprecision;
5. and publication bias.

We graded the overall strength of evidence for each outcome as 'high', 'moderate', 'low' or 'very low', and resolved any disagreement through discussion or by consulting a third author (TF or NW).

We included the following outcomes in the summary of findings tables.

- Recurrence of any episode at one year:
  - hospitalization for any mood episodes;
  - YMRS total score ≥15 for manic episode;
  - MADRS total score ≥15 for depressive episode; and HDRS total score ≥14 for depressive episode;
  - clinical worsening with the need for addition of a mood stabilizer, antidepressant treatment, antipsychotic medication or benzodiazepine; or
  - active suicidal behavior.
- Withdrawal from treatment due to any reason:
  - short term, up to 12 weeks after treatment initiation (range: 7 to 16 weeks);
  - long term, at least six months after treatment initiation (range: 6 to 16 months).

Results

Description of studies

Lamotrigine in the maintenance treatment of bipolar disorder

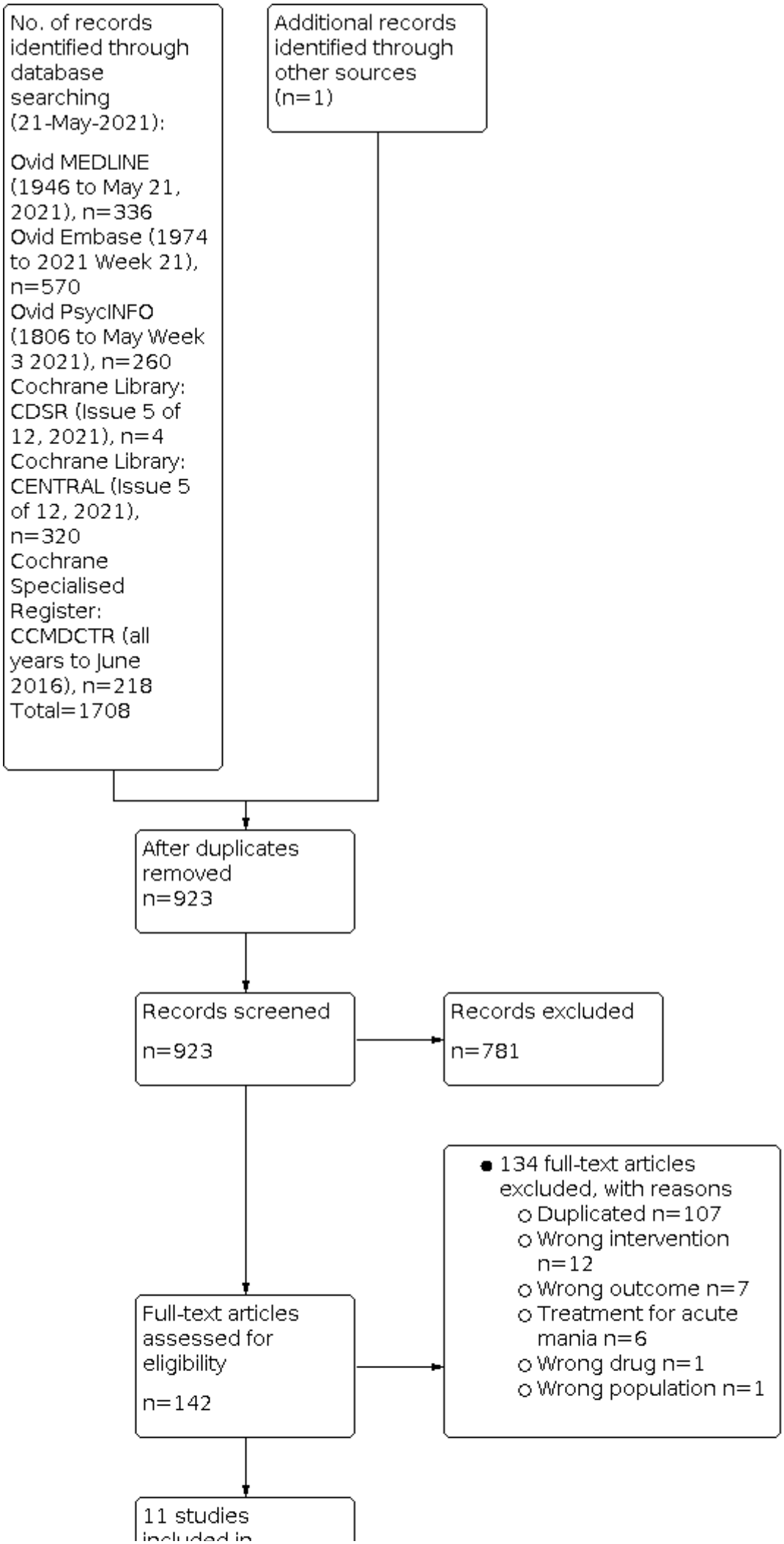
Results of the search

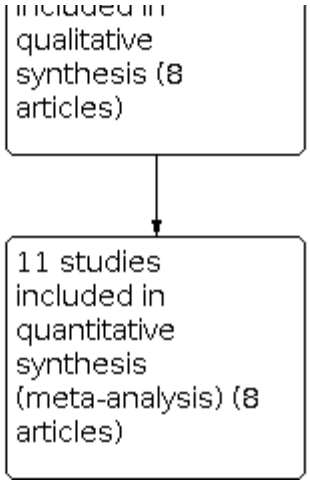
Searches of the Cochrane Library (CENTRAL and CDSR), MEDLINE, Embase, PsycINFO, and CCMDCTR databases yielded a total of 1708 records (updated to include searches up to May 2021). Koyama 2011 written in Japanese was not retrieved by searching these electrical database, but from screening of the reference list of Oya 2019. Of those initial 1709 studies,

we identified 142 studies as potentially eligible for inclusion after title and abstract screening. We retrieved full-text articles for these 142 studies for full inspection, of which 134 were excluded and finally, 11 studies (eight papers) fulfilled our inclusion criteria and were included in the review. Our study selection process is illustrated in Figure 1 (Moher 2009).

Figure 1

Open in figure viewer


No. of records identified through database searching (21-May-2021):
Ovid MEDLINE (1946 to May 21, 2021), n=336
Ovid Embase (1974 to 2021 Week 21), n=570
Ovid PsycINFO (1806 to May Week 3 2021), n=260
Cochrane Library: CDSR (Issue 5 of 12, 2021), n=4
Cochrane Library: CENTRAL (Issue 5 of 12, 2021), n=320
Cochrane Specialised Register: CCMDCTR (all years to June 2016), n=218
Total=1708
Additional records identified through other sources (n=1)
After duplicates removed n=923
Records screened n=923
Records excluded n=781
Full-text articles assessed for eligibility n=142
134 full-text articles excluded, with reasons
Duplicated n=107
Wrong intervention n=12
Wrong outcome n=7
Treatment for acute mania n=6
Wrong drug n=1
Wrong population n=1
11 studies



PRISMA flow diagram.

Included studies

Please refer to Characteristics of included studies for further information.

We included 11 studies in this review (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Koyama 2011; Licht 2010; Suppes 2008a). We identified one publication which reported findings from five RCTs; of these, one (GW602/SCAB2001) was the duplication of Calabrese 1999. Therefore, this was excluded and the remaining four studies were included in this review (Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]). Please note we have listed these trial names as per the original publication.

Study design and settings

All included studies were multicenter randomized trials; all but one study applied double-blind methodology (Suppes 2008a). We did not identify any cluster-randomized studies.

Study duration

The length of study ranged from seven to 302 weeks: Calabrese 1999, seven weeks; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910], eight weeks; Calabrese 2008 [GW603/SCAA2010], 10 weeks. Treatment duration ranged from 16 weeks to 5.8 years: Suppes 2008a, 16 weeks; Koyama 2011, 26 weeks; Calabrese 2000, six months; Bowden 2003 and Calabrese 2003, 76 weeks; and in Licht 2010 treatment continued for 5.8 years. Our analysis was stratified according to the study period (short term and long term). We defined study duration of seven to 16 weeks as "short term" and duration of over six months as "long term".

Sample sizes

The 11 included studies involved a total 2314 participants: 1146 were randomized to lamotrigine, 869 were randomized to placebo and 299 to lithium.

Bowden 2003, Calabrese 2003, Licht 2010, and Koyama 2011 were the only studies that reported sample size calculations.

Participants

Of the 11 included studies, participants were diagnosed with bipolar I disorder in seven studies (Bowden 2003; Calabrese 1999; Calabrese 2003; Koyama 2011; Licht 2010; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]). Participants from Calabrese 2000, and Calabrese 2008 [GW603/SCAA2010] were diagnosed with bipolar I as well as bipolar II disorders. Two studies included patients with bipolar II disorder (Calabrese 2008 [SCA100223]; Suppes 2008a).

In the open-label phase, 38.5% of participants were treated with lamotrigine prior to double-blinded randomization phase (Bowden 2003; Calabrese 2000; Calabrese 2003; Koyama 2011); in Calabrese 2008 [SCA40910], the proportion of pre-randomization use of lamotrigine was 53.9%. No description of medications used prior to randomization was available in Calabrese 1999, Calabrese 2008 [GW603/SCAA2010], Licht 2010, Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]. Only Suppes 2008a was a single-blind randomized study. Therefore, it was an open-label study throughout the study duration (4.1%).

Participants included in each of the 11 included studies were hospital outpatients of both genders; in six studies, participants were aged at least 18 years old (Bowden 2003; Calabrese 2003; Calabrese 1999; Calabrese 2000; Licht 2010; Suppes 2008a). The inclusion criterion for Koyama 2011 was limited to adults aged 20 years or above (Koyama 2011). In the remaining four studies, no description of specific age range/cut-offs were provided besides describing their participants as “adults” (Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]).

All the study participants were diagnosed with bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-IV, DSM-IV-TR), assessed by a variety of instruments including the Structured Clinical Interview for DSM Disorders (SCID) as illustrated in Calabrese 1999 and Suppes 2008a.

Interventions and comparators

Types of comparisons were as follows: seven studies comparing lamotrigine with placebo (Calabrese 1999; Calabrese 2000; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Koyama 2011), two investigated lamotrigine versus lithium (Licht 2010; Suppes 2008a), and two were three-arm studies comparing lamotrigine with lithium as well as placebo (Bowden 2003; Calabrese 2003).

During the open-label phase, the dosing schedule of lamotrigine used in Suppes 2008a was as follows: weeks 1 to 2, 25 mg/day; weeks 3 to 4, 50 mg/day; week 5, 75 mg/day; week 6, 100 mg/day; week 7, 150 mg/day; and week 8, 200 mg/day. In the other included studies, lamotrigine dose was escalated to reach a target dose as follows: weeks to -2, 25 mg/day; weeks 3 to 4, 50 mg/day; week 5, 10 0mg/day; and week 6, 200 mg/day. After six weeks, the daily dose was adjusted depending on tolerability, with a flexible dosing regimen from 100 mg to 500 mg daily in the maintenance phase.

Outcomes

The 11 included studies reported the following outcome measures.

1. Recurrence of manic episodes at one year measured by the Young Mania Rating Scale (YMRS) (Suppes 2008a) and Mania Rating Scale (MRS) (Calabrese 1999; Calabrese 2000; Calabrese 2003).
2. Recurrent of depressive episodes at one year by the Hamilton Depression Rating Scale (HDRS) (Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Suppes 2008a).

3. Addition of any psychotropics for recurrence of any episodes at one year (Bowden 2003; Calabrese 2003; Calabrese 2000; Koyama 2011; Licht 2010).
4. Active suicidal behavior (Licht 2010).
5. Withdrawal from treatment by any reason up to 12 weeks after the intervention i.e. short-term withdrawal (Calabrese 1999).
6. Withdrawal from treatment due to any reason at six- to12 months after the intervention i.e. long-term withdrawal (Bowden 2003; Calabrese 2000; Calabrese 2003; Koyama 2011; Licht 2010; Suppes 2008a).
7. Any reported adverse effects (number of participants who experienced at least one adverse effect) up to 12 weeks after the intervention i.e. short-term safety (Calabrese 1999; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]).
8. Any reported adverse effects (number of participants who experienced at least one adverse effect) six to 12 months after the intervention i.e. long-term safety (Bowden 2003; Calabrese 2003; Calabrese 2000; Koyama 2011; Licht 2010; Suppes 2008a).
9. Recurrence of manic episode (Bowden 2003; Calabrese 2003; Koyama 2011; Licht 2010).
10. Recurrence of depressive episode (Bowden 2003; Calabrese 2003; Koyama 2011; Licht 2010).

None of the included studies reported data on quality of life or satisfaction with treatment outcomes.

Excluded studies

We excluded 27 studies from this review (see Figure 1). The most common reason of exclusion was inappropriate study inclusion criteria. Other reasons were wrong type(s) of intervention(s), wrong outcome measures, wrong study designs (e.g. non-randomized controlled trials (RCTs)), and the lack of relevant data (Characteristics of excluded studies).

Risk of bias in included studies

Findings of our assessment of risk of bias in included studies are illustrated in Figure 2 and Figure 3 for the specific judgments. Further details and justification of our judgments are presented in the Characteristics of included studies section.

Figure 2 **Open in figure viewer**

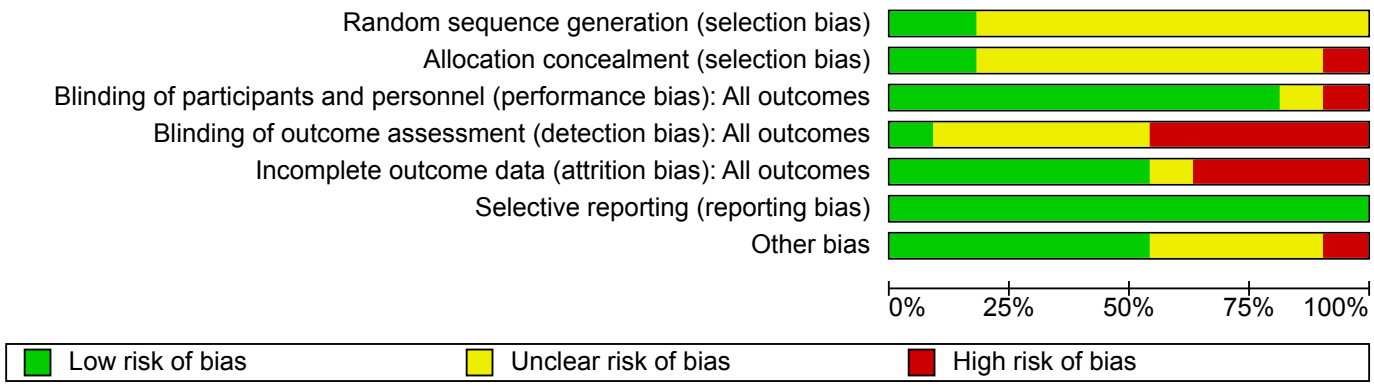


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3

Open in figure viewer

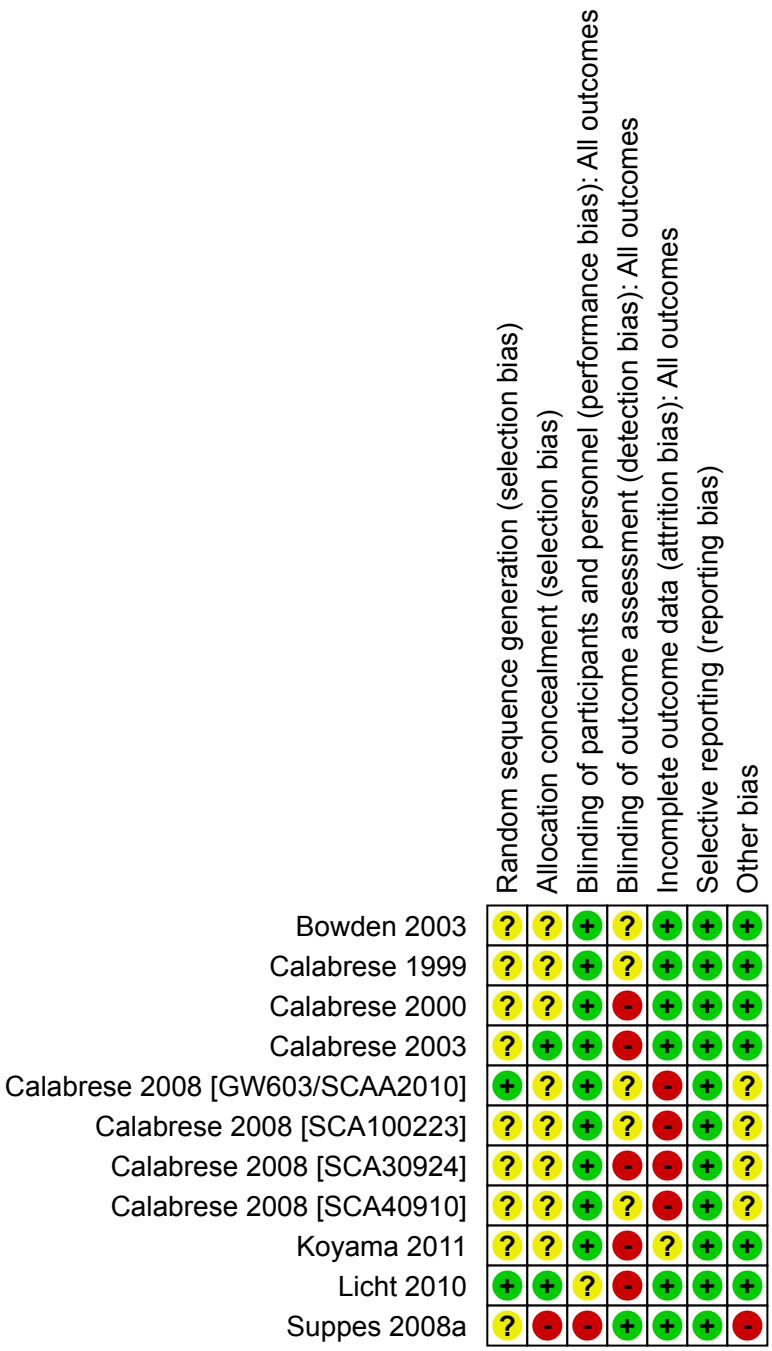


Figure 3. Risk of bias table

Allocation

Nine studies did not report details on the sequence generation and were judged as having an unclear risk of bias (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Koyama 2011; Suppes 2008a). Two studies provided sufficient information on sequence generation (Calabrese 2008 [GW603/SCAA2010]; Licht 2010).

Eight studies failed to provide details on how allocation was concealed and were thus judged as having an unclear risk of bias (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Koyama 2011). Two studies provided sufficient information on allocation concealment and we judged them as having low risk of bias (Calabrese 2003; Licht 2010). Suppes 2008a was described as an open-label study and thus we classified it as high risk of bias.

Blinding

Blinding of participants and personnel (performance bias)

We classified nine studies included in the review as being at low risk of performance bias, as participants and personal were explicitly described as blinded in the study report (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Koyama 2011). We classified one trial as being unclear because it provided no information on blinding participants or personnel (Licht 2010). Suppes 2008a was described as an open-label study and thus we classified it as high risk of bias.

Blinding of outcome assessors (detection bias)

We rated one trial as having a low risk of detection bias (Suppes 2008a); five trials as having a high risk of detection bias (Calabrese 2000; Calabrese 2003; Calabrese 2008 [SCA30924] Koyama 2011; Licht 2010). The remaining trials did not provide details on the blinding of outcome assessors and thus were judged to be of unclear risk of bias (Bowden 2003; Calabrese 1999; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA40910]).

Incomplete outcome data

We rated six trials to be adequate in terms of addressing incomplete outcome data (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Licht 2010; Suppes 2008a). One trial had unclear risk of attrition bias (Koyama 2011), and the remaining four trials were assessed to be at high risk of bias since they lacked clear description of study methodology (Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]).

Selective reporting

On the whole, study authors diligently reported study data and thus we assessed all included studies to be at low risk of reporting bias (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [GW603/SCAA2010]; Koyama 2011; Licht 2010; Suppes 2008a; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]).

Other potential sources of bias

We did not identify other potential sources of bias amongst the 11 included studies.

Effects of interventions

See: **Summary of findings 1** Lamotrigine versus placebo for the maintenance treatment of bipolar disorder; **Summary of findings 2** Lamotrigine versus lithium for the maintenance treatment of bipolar disorder

Comparison 1: Lamotrigine versus no treatment

See summary of findings Table 1.

Primary outcomes

Hospitalization for any mood episode

No trial measured this outcome.

Young Mania Rating Scale (YMRS) total score ≥ 15 for manic episode

Three trials provided data on the YMRS total score ≥ 15 for manic episode, enrolling a total of 663 participants. But only one study contributed to the meta-analysis because the other two studies had zero events. We found a difference between lamotrigine and placebo (RR 0.67, 95% CI 0.51 to 0.87; P = 0.003) in favor of lamotrigine; low-certainty evidence (Analysis 1.1).

Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 15 depressive episode; Hamilton Depression Rating Scale (HDRS) total score ≥ 14 for depressive episode

Seven trials provided data on the MADRS total score ≥ 15 for depressive episodes or HDRS total score ≥ 14 for depressive episodes, including a total of 1606 participants. There was no difference between lamotrigine and placebo (RR 0.85, 95% CI 0.70 to 1.02; P = 0.08; low-certainty evidence Analysis 1.2), with substantial heterogeneity (I^2 = 71%; P = 0.002).

Clinical worsening with the need for additional treatment (mood stabilizers, antidepressants, antipsychotics or benzodiazepines)

Four trials (n=756) provided data on clinical worsening with the need of additional treatment. We found a difference between lamotrigine and placebo (RR 0.82, 95% CI 0.70 to 0.98; P = 0.03) in favor of lamotrigine; moderate-certainty evidence (Analysis 1.3). Heterogeneity was found to be not important (I^2 = 31%; P = 0.23).

Active suicidal behavior

None of the included trials measured this a priori outcome.

Withdrawal from treatment due to any reason (short term)

Only one trial of 195 participants provided data on treatment withdrawal due to any reason (short term), and we found no difference between lamotrigine and placebo (RR 1.10, 95% CI 0.70 to 1.74; P = 0.67; very low-certainty evidence Analysis 1.4).

Withdrawal from treatment due to any reason (long term)

Four trials of 700 participants assessed treatment withdrawal due to any reason (long term). Treatment of lamotrigine was associated with a reduced incidence of treatment withdrawal as compared to placebo (RR 0.88, 95% CI 0.78 to 0.99; P = 0.03; moderate-certainty evidence Analysis 1.5), with moderate heterogeneity (I^2 = 37%; P = 0.19).

Adverse effects (short term)

Five trials reported adverse effects (short term), enrolling a total of 1138 participants. There was no difference between lamotrigine and placebo (RR 1.07, 95% CI 0.81 to 1.42; P = 0.61; very low-certainty evidence Analysis 1.6); heterogeneity was moderate (I^2 = 42%; P = 0.14).

Adverse effects (long term)

Four trials provided data on adverse effects (long term), including a total of 756 participants. We found no difference between the two groups (RR 0.97, 95% CI 0.77 to 1.23; P = 0.83; moderate-certainty evidence Analysis 1.7), with moderate heterogeneity (I^2 = 45%; P = 0.14).

Secondary outcomes

Recurrence of manic episode at one year

Three trials of 574 participants assessed recurrence of manic episode. We found no difference between lamotrigine and placebo (RR 0.91, 95% CI 0.66 to 1.26; P = 0.58; moderate-certainty evidence Analysis 1.8). We found no heterogeneity (I^2 = 0%; P = 0.59).

Recurrence of depressive episode at one year

Three trials provided data on the recurrence of depressive episode, enrolling a total of 574 participants. We found a difference between lamotrigine and placebo (RR 0.75, 95% CI 0.53 to 1.05; P = 0.09) in favor of lamotrigine moderate-certainty evidence (Analysis 1.9). Heterogeneity was moderate for this outcome (I^2 = 37%; P = 0.21).

Quality of life

No trial measured this outcome.

Total severity score

No trial measured this outcome.

Comparison 2: Lamotrigine versus lithium

See summary of findings Table 2.

Primary outcomes

Hospitalization for any mood episode

No trial measured this outcome.

Young Mania Rating Scale (YMRS) total score ≥ 15 for manic episode

Two trials of 376 participants provided data on the YMRS total score 15 or greater for manic episode and there was no difference between the two groups. (RR 3.57, 95% CI 0.15 to 85.39; P = 0.43; very low-certainty evidence Analysis 2.1). Heterogeneity was not applicable.

Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 15 depressive episode; Hamilton Depression Rating Scale (HDRS) total score ≥ 14 for depressive episode

Two trials reported the MADRS total score ≥ 15 for depressive episode or HDRS total score ≥14 for depressive episode, including a total of 376 participants. We found no difference between lamotrigine and placebo (RR 1.40, 95% CI 0.70 to 2.79; P = 0.34; low-certainty evidence Analysis 2.2). Heterogeneity was not applicable.

Clinical worsening with the need for additional treatment (mood stabilizers, antidepressants, antipsychotics or benzodiazepines)

Three trials of 602 participants assessed clinical worsening with the use of additional treatment. There was no difference between lamotrigine and lithium (RR 1.11, 95% CI 0.92 to 1.35; P = 0.28; moderate-certainty evidence Analysis 2.3). We found no important heterogeneity (I^2 = 0%; P = 0.73).

Active suicidal behavior

We identified just one trial (n = 155) with data on active suicidal behavior. There was no difference between lamotrigine and placebo (RR 1.01, 95% CI 0.06 to 15.91; P = 0.99; very low-certainty evidence Analysis 2.4).

Withdrawal from treatment due to any reason (short term)

None the included trials measured this pre-specified outcome.

Withdrawal from treatment due to any reason (long term)

Four trials provided data on treatment withdrawal due to any reason (long term), including a total of 636 participants. No difference between groups was observed (RR 0.96, 95% CI 0.88 to 1.05; P = 0.34; moderate-certainty evidence Analysis 2.5); heterogeneity was found to be minimal (I^2 = 4%; P = 0.37).

Adverse effects (short term)

None of the included trial measured this outcome.

Adverse effects (long term)

Four trials assessed long-term adverse effect amongst 691 participants. We found a difference between lamotrigine and lithium (RR 0.70, 95% CI 0.51 to 0.96; P = 0.02) in favor of lamotrigine moderate-certainty evidence (Analysis 2.6). Heterogeneity was found to be moderate (I^2 = 37%; P = 0.19).

Secondary outcomes

Recurrence of manic episode at one year

Three trials provided data on the recurrence of manic episode, including a total of 602 participants. We noted a higher incidence of recurrent manic episode with lamotrigine versus lithium (RR 2.13, 95% CI 1.32 to 3.44; P = 0.002; moderate-certainty evidence Analysis 2.7), with no heterogeneity (I^2 = 0%; P = 0.43).

Recurrence of depressive episode at one year

Three trials (602 participants) assessed the recurrence of depressive episode. There was no difference between the two groups (RR 0.83, 95% CI 0.63 to 1.09; P = 0.18; moderate-certainty evidence Analysis 2.8). We found no important heterogeneity (I^2 = 2%; P = 0.36).

Quality of life

None of the included trials measured this outcome.

Total severity score

None of the included trials measured this a priori outcome.

Discussion

Summary of main results

Our review included 11 studies involving 2314 participants. We found low-certainty evidence supporting the use of lamotrigine over placebo for people with bipolar disorder. Lamotrigine was found to be more effective than placebo for minimizing recurrence of bipolar depression at one year. Moderate-certainty evidence indicated that lamotrigine a similar safety profile compared to placebo. Treatment withdrawal at 6 to 12 months was more frequent amongst participants in the placebo groups when compared with the lamotrigine groups.

Compared to lithium, we found low-certainty evidence indicating that lamotrigine was comparable to lithium in the outcomes of bipolar disorder symptoms except for recurrence of bipolar mania. Current evidence also found that lamotrigine increased incidence of exacerbated bipolar manic symptoms when compared to lithium. In addition, adverse events experienced by participants treated with lamotrigine were lower than those reported in the lithium groups.

Overall completeness and applicability of evidence

We conducted a comprehensive and systematic literature search to identify all available published and unpublished studies fulfilling our pre-specified inclusion criteria, and 11 studies were eventually included. Of these, seven studies compared lamotrigine with placebo, two were three-arm studies that investigated the effects of lamotrigine versus lithium versus placebo, and the remaining two studies compared lamotrigine with lithium.

Overall, all the included studies reported our efficacy outcomes of interest. We performed data conversion (from continuous to dichotomous data) using indicated average, standard deviation, and sample numbers (Bowden 2003; Calabrese 1999; Calabrese 2000; Calabrese 2003; Calabrese 2008 [GW603/SCAA2010]; Calabrese 2008 [SCA100223]; Calabrese 2008 [SCA30924]; Calabrese 2008 [SCA40910]; Suppes 2008a). As a result, we were able to synthesize evidence for the various efficacy outcomes in the comparisons of lamotrigine versus placebo and lamotrigine versus lithium. None of the included studies assessed hospitalization for any mood episode, quality of life, or total change score Young Mania Rating Scale (YMRS) plus: Hamilton Depression Rating Scale (HDRS)). Reporting of adverse events was generally adequate, which allowed for evaluation of safety outcomes.

All our studies enrolled adults with clinically-diagnosed bipolar disorder (as confirmed by: Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV)) and were conducted in the outpatient setting from several countries.

In this review we attempted to ensure the highest possible level of certainty of the evidence, we excluded non-randomized studies or randomized controlled trials (RCTs) that did not use a standard diagnostic process. Our review findings showed that lamotrigine was more effective than placebo on recurrence of bipolar disorder, and the incidence of adverse events was comparable between groups. Furthermore, lamotrigine was found to be more tolerable than lithium, which has been the standard treatment approach in clinical practice. The key to treatment during the maintenance phase of bipolar disorder is continuity of treatment. Considering these facts, we would like to highlight that lamotrigine poses as a viable treatment option.

Quality of the evidence

We assessed the certainty of the evidence collected using the GRADE approach, which takes into consideration five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Elaboration of our GRADE assessment for each outcome is illustrated in summary of findings Table 1 and summary of findings Table 2.

Overall GRADE assessment

- Lamotrigine versus placebo: evidence on efficacy outcomes was generally of low to moderate certainty. Overall, the number of included studies was small and thus we could not assess publication bias. Included evidence regarding adverse effects of lamotrigine was judged to be of very low certainty in the short-term duration and of moderate certainty in the long term.
- Lamotrigine versus lithium: certainty of evidence on efficacy outcomes was moderate. Only limited study findings were available and we decided to not investigate publication bias. Certainty of evidence on the comparative adverse effect profiles of lamotrigine was assessed to be moderate.

Risk of bias

We rated all included studies as having an unclear risk of bias in at least one domain of the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2020), with the most commonly observed weakness being selection bias (random sequence generation and allocation concealment). We judged seven of the nine included studies as having a high risk of bias in at least one domain; among these, six studies showed a high risk of detection bias (blinding of outcome assessment). These potential biases pose a major threat to the validity of the review findings.

Inconsistency

Substantial statistical heterogeneity across studies was noted in the outcome of recurrence of any episodes at one year (MADRS total score ≥15 for depressive episode or HDRS total score ≥14 for depressive episode) for the comparison of lamotrigine versus placebo, which limited the reliability of the included evidence and we downgraded the level of certainty accordingly.

Indirectness

Overall, the available evidence matched well with our pre-defined clinical questions and review scope. The included study subjects were all hospital outpatients during the maintenance phase of bipolar I or II disorder.

Imprecision

The precision of our outcome estimates was significantly hampered by several factors, such as very wide confidence intervals and small size of some of studies.

Publication bias

We did not assess publication bias using a funnel plot as none of the analyses included more than 10 studies.

Potential biases in the review process

We conducted an extensive search for randomized studies meeting our pre-defined eligibility criteria. Nevertheless, we found insufficient data available to fully answer our review questions and numerous outcomes had only a small number of included studies. As a result, we were unable to conduct subgroup analyses and sensitivity analyses as planned at the protocol stage; however, we did not find any sources of bias that might be expected to affect the study results. On the other hand, of the 11 studies we included, eight were funded by the same sponsor and thus we cannot rule out the potential of industry sponsorship bias, which could lead to an overestimation of interventions.

Agreements and disagreements with other studies or reviews

Our results are consistent with the results of four previous systematic reviews (Beynon 2009; Miura 2014; Oya 2019; Smith 2007). Lamotrigine was shown to be superior over placebo in reducing relapse of any mood episode. Although lamotrigine showed no benefits in bipolar manic episode, lamotrigine was more effective than placebo in reducing bipolar depressive episode (Beynon 2009; Smith 2007). As for adverse effects, lamotrigine was found to be better tolerated than lithium (Miura 2014; Smith 2007).