TECHNICAL COMMENTARY

Lamotrigine

Introduction

Lamotrigine is an anticonvulsant used primarily in the treatment of seizure disorders such as epilepsy. Anticonvulsant medications influence the actions of neurotransmitters leading to a decrease in brain cell (neuron) excitability. In bipolar disorder, lamotrigine is used mainly for the treatment of depression.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven reviews that met our inclusion criteria[3-9].

- Compared to placebo, high quality evidence finds a small effect of fewer relapses with lamotrigine to any mood state in stable patients.
- Moderate to high quality evidence found a small effect of greater improvement in depression symptoms, but not mania symptoms with mono or adjunctive lamotrigine than with placebo, and no differences in adverse events, including switching to mania.
- Compared to other medications, moderate to high quality evidence suggests lamotrigine is less effective than tamoxefin, risperidone, haloperidol or olanzapine for acute mania symptoms. There was more discontinuation with lamotrigine than with olanzapine.
- Moderate to low quality evidence suggests more switching to mania with lamotrigine than with quetiapine or ziprasidone.

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- Moderate to low quality evidence suggests fewer relapses with quetiapine than with lamotrigine, and lamotrigine was better tolerated than carbamazepine or lithium + valproate.
- Moderate quality evidence suggests the rate of adverse dermatological reaction with lamotrigine is around 8.6%, with rates of Stevens-Johnson syndrome/toxic epidermal necrolysis in particular being around 0.02%.
- There were no differences in symptoms or adverse events when lamotrigine was compared to lithium, olanzapine + fluoxetine, trancylpromine, citalopram, or inositol.

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Azorin JM, Bowden CL, Garay RP, Perugi G, Vieta E, Young AH

Possible new ways in the pharmacological treatment of bipolar disorder and comorbid alcoholism

Neuropsychiatric Disease and Treatment 2010; 6: 37-46

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Comparison	**Adjunctive lamotrigine (25 mg/day titrated to 300 mg/day).**
Summary of evidence	**Low quality evidence (small sample) is unable to determine the benefits or harms of adjunctive lamotrigine for people with bipolar disorder and alcohol dependence).**
Alcohol consumption	
There were significant decreases in alcohol consumption with adjunctive lamotrigine; 1 open-label trial (N = 28) found an average 40% reduction in carbohydrate deficient transferrin, a 32.5% reduction in craving measures, and a 67.7% reduction in the number of drinks per week over the course of the trial (24 weeks).	
Symptoms	
There were significant improvements in symptoms with adjunctive lamotrigine; 1 open-label trial (N = 28) found an average 54.4% improvement in overall symptoms, a 40.8% improvement in mania symptoms, and a 31.4% improvement in depression symptoms over the course of the trial (24 weeks).	
Risks	There were no drop-outs due to adverse events.
Consistency in results‡	Not applicable (1 trial).
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct measures.

Bloom R, Amber KT

Identifying the incidence of rash, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients taking lamotrigine: A systematic review of 122 randomized controlled trials

Anais Brasileiros de Dermatologia 2017; 92: 139-41

View review abstract online	
Comparison	**Monotherapy lamotrigine vs. placebo**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests the rate of adverse dermatological reaction with lamotrigine is around 8.6%, with rates of Stevens-Johnson syndrome/toxic epidermal necrolysis being around 0.02%.**
Risks	
122 RCTs (N = 9,947 patients with bipolar disorder) found 8.6% of patients experienced an adverse dermatologic reaction, with 0.02% experiencing Stevens-Johnson syndrome/toxic epidermal necrolysis.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct assessments.

Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A, Geddes JR, Kanba S

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis

The Lancet Psychiatry 2014; 1: 351-9

View review abstract online

Comparison 1	**Lamotrigine vs. placebo.** **Authors rate the quality of evidence as low.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, imprecise, some indirectness) suggests a small effect of reduced relapse to depression, but not mania, with lamotrigine compared to placebo.**
Any relapse	
A small, significant effect of lower risk of relapse with lamotrigine; N = 541, RR = 0.76, 95%CI 0.62 to 0.94, $p < 0.05$	

Mania/mixed relapse	
No significant differences between groups; N = 541, RR = 0.90, 95%CI 0.60 to 1.34, $p > 0.05$	
Depression relapse	
A small, significant effect of lower risk of relapse with lamotrigine; N = 541, RR = 0.69, 95%CI 0.50 to 0.94, $p < 0.05$	
Risks	There were no differences in tolerability (RR = 0.69, 95%CI 0.21 to 2.35) or acceptability (RR = 0.84, 95%CI 0.67 to 1.03).
Consistency in results	Authors report that data are consistent.
Precision in results	Precise for any relapse, imprecise for other outcomes.
Directness of results	Some indirectness
Comparison 2	**Lamotrigine vs. olanzapine or quetiapine.**
Summary of evidence	**Moderate to low quality evidence (consistent, some imprecision and indirectness) suggests fewer relapses with olanzapine or quetiapine than with lamotrigine lamotrigine, and lamotrigine was better tolerated than carbamazepine, lithium, or lithium + valproate.**
Any relapse	
Small effects of fewer relapses with olanzapine or quetiapine than with lamotrigine; Lamotrigine vs. olanzapine: RR = 0.66, 95%CI 0.48 to 0.89, $p < 0.05$ Lamotrigine vs. quetiapine: RR = 0.69, 95%CI 0.50 to 0.96, $p < 0.05$	
Risks	Lamotrigine was significantly better tolerated than carbamazepine (RR = 5.24, 95%CI 1.07 to 26.32), lithium (RR = 3.76, 95%CI 1.13 to 12.66), and lithium + valproate (RR = 5.95, 95%CI 1.02 to 33.33), 5·95 (1·02–33·33).
Consistency in results	Authors report that data are consistent.
Precision in results	Precise for relapse, imprecise for risks.
Directness of results	Indirect (network meta-analysis)

Oya K, Sakuma K, Esumi S, Hashimoto Y, Hatano M, Matsuda Y, Matsui Y, Miyake N, Nomura I, Okuya M, Iwata N, Kato M, Hashimoto R, Mishima K, Watanabe N,

Kishi T

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

Neuropsychopharmacology Reports 2019; 39: 241-6

View review abstract online

Comparison	**Lamotrigine vs. placebo in people with bipolar disorder in a stable state.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small effect of fewer relapses with lamotrigine.**
Relapse	
A small effect of fewer relapses with lamotrigine; 4 RCTs, N = 706, RR = 0.81, 95%CI 0.70 to 0.93, p = 0.004, I^2 = 0%	
Risks	There was less all-cause discontinuation with lamotrigine.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Solmi M, Veronese N, Zaninotto L, Van Der Loos MLM, Gao K, Schaffer A, Reis C, Normann C, Anghelescu IG, Correll CU

Lamotrigine compared to placebo and other agents with antidepressant activity in patients with unipolar and bipolar depression: A comprehensive meta-analysis of efficacy and safety outcomes in short-term trials

CNS Spectrums 2017; 21: 403-18

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Comparison 1	**Mono or adjunctive lamotrigine (+ antidepressants or mood stabilisers) vs. placebo.** **The sample included people with unipolar depression.**
Summary of evidence	**Moderate to high quality evidence (large sample, indirect,**

	consistent, precise) suggests a small effect of greater improvement in depression symptoms with mono or adjunctive lamotrigine than with placebo, with no differences in adverse events.
Depression symptoms and clinical response	
A small, significant effect of greater improvement in depression symptoms with lamotrigine; 11 RCTs, N = 1,409, SMD = -0.15, 95%CI -0.27 to -0.02, $p = 0.02$, $I^2 = 22\%$, $p = 0.24$ *A small, significant effect of greater clinical response with lamotrigine (after removing one extreme outlier);* 7 RCTs, RR = 1.42, 95%CI 1.13 to 1.78, $p = 0.003$, $I^2 = 2\%$, $p = 0.08$ *There were no differences in remission rates;* 3 RCTs, RR = 0.82, 95%CI 0.30 to 2.24, $p = 0.70$, $I^2 = 55\%$, $p = 0.11$ Lamotrigine's efficacy for depressive symptoms did not differ according to dose, sex, age, baseline symptom scores, study duration, monotherapy vs. augmentation studies, bipolar vs. unipolar depression samples, double vs. single-blind studies, or industry vs. non-industry sponsored trials. Studies with smaller samples reported larger effect sizes. Authors report no evidence of publication bias.	
Comparison 2	**Monotherapy or adjunctive lamotrigine (+ antidepressants or mood stabilizers) vs. lithium, olanzapine + fluoxetine, trancylpromine, citalopram, or inositol.**
Summary of evidence	**Moderate to high quality evidence (large sample, indirect, consistent, precise) suggests no differences between groups in symptoms or adverse events.**
Depression symptoms	
No significant differences between groups; 6 RCTs, N = 624, SMD = 0.02, 95%CI -0.24 to 0.28, $p = 0.88$, $I^2 = 36\%$, $p = 0.17$ Lamotrigine's efficacy for depressive symptoms did not differ according to monotherapy vs. augmentation trials, bipolar vs. unipolar depression samples, or comparison drug type. Authors report no evidence of publication bias.	
Risks	Adverse effects, switch to mania, and all-cause/specific-cause discontinuation were similar across all comparisons.
Consistency in results	Consistent
Precision in results	Precise for SMDs, imprecise for RRs.
Directness of results	Indirect for samples (bipolar and unipolar combined) and for comparison 2 (mixed control conditions), although subgroup

	analyses showed no differences in results according to diagnosis or comparison drug type.

Taylor DM, Cornelius V, Smith L, Young AH

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

Acta Psychiatrica Scandinavica 2014; 130: 452-69

View review abstract online

Comparison 1	**Lamotrigine vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests significant, small effects of greater improvement in depression symptoms and better response to treatment with lamotrigine than with placebo. There were no differences between groups in rates of switching to mania or withdrawal from treatment (for any reason).**
Depression symptoms	
Significant, small effect of greater improvement in depression symptoms with lamotrigine; 5 RCTs, N = 1195, SMD = -0.17, 95%CI -0.32 to -0.02, $p < 0.05$	
Response	
Significant, small effect of better treatment response with lamotrigine; 5 RCTs, N = 1195, OR = 1.56, 95%CI 1.23 to 1.97, $p < 0.05$	
Switch to mania	
No significant differences between groups; 5 RCTs, N = 1195, OR = 2.34, 95%CI 0.44 to 12.50, $p > 0.05$	
Risks	There were no differences between groups in rates of withdrawal from treatment (any reason).
Consistency in results	Authors report data are consistent.
Precision in results	Precise for depression symptoms only.
Directness of results	Direct (pairwise comparisons).
Comparison 2	**Lamotrigine vs. other medications.**

Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests small effects of greater improvement in depression symptoms and greater response to treatment with olanzapine+fluoxetine than with lamotrigine.** **Moderate to low quality evidence (unclear sample size, consistent, imprecise, indirect) suggests more switching to mania with lamotrigine than with quetiapine or ziprasidone.**
Depression symptoms	
A significant, small effect of greater improvement in depression symptoms with olanzapine + fluoxetine than with lamotrigine; 1 RCT, N = 410, SMD = 0.28, 95%CI 0.09 to 0.48, $p < 0.05$ *No significant differences between lamotrigine and SSRI antidepressant;* 1 RCT, N = 20, SMD = 0.09, 95%CI -0.91 to 0.99, $p > 0.05$	
Response	
A significant, small effect of greater response to treatment with olanzapine + fluoxetine than with lamotrigine; 1 RCT, N = 410, OR = 0.67, 95%CI 0.44 to 1.00, $p < 0.05$ *There were no significant differences between lamotrigine and SSRI antidepressant;* 1 RCT, N = 20, OR = 0.44, 95%CI 0.07 to 2.67, $p > 0.05$	
Switch to mania	
There were no significant differences between lamotrigine and olanzapine + fluoxetine; 1 RCT, N = 410, OR = 1.25, 95%CI 0.48 to 3.23, $p > 0.05$ *There were no significant differences between lamotrigine and SSRI antidepressant;* 1 RCT, N = 20, OR = 1.05, 95%CI 0.05 to 18.60, $p > 0.05$ *The network (indirect) meta-analysis found more switching to mania with lamotrigine than with quetiapine or ziprasidone;* Quetiapine: OR = 4.66, 95%CI 1.21 to 12.20, $p < 0.05$ Ziprasidone: OR = 9.99, 95%CI 1.04 to 40.70, $p < 0.05$	
Consistency in results	Authors report data are consistent.
Precision in results	Precise for depression symptoms and response, olanzapine + fluoxetine comparison only.
Directness of results	Direct, apart from network meta-analysis results.

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Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ

A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania

Psychological Medicine 2015; 45: 299-317

View review abstract online

Comparison	**Lamotrigine vs. placebo or other medications.**
Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, mostly precise, some indirectness) suggests lamotrigine is less effective than tamoxefin, risperidone, haloperidol or olanzapine for acute mania symptoms. There was more discontinuation with lamotrigine than with olanzapine. There were no significant differences in acute mania symptoms between lamotrigine and placebo or other medications.**
Acute mania symptoms	
No significant differences between lamotrigine and placebo; Network meta-analysis: 57 studies, N = 14,256, SMD = 0.13, 95%CrI -0.16 to 0.44, $p > 0.05$ *A large, significant effect of lamotrigine being less effective than tamoxefin;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.78, 95%CrI 2.18 to 3.41, $p < 0.05$ *A medium-sized, significant effect of lamotrigine being less effective than risperidone;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.51, 95%CrI 0.14 to 0.87, $p < 0.05$ *A medium-sized, significant effect of lamotrigine being less effective than haloperidol;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.40, 95%CrI 0.06 to 0.73, $p < 0.05$ *A small, significant effect of lamotrigine being less effective than olanzapine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.35, 95%CrI 0.02 to 0.66, $p < 0.05$ Authors report no other significant differences between lamotrigine and other medications.	
Risks	*More discontinuation with lamotrigine than with olanzapine;* Network meta-analysis; OR = 0.37, 95%CI 0.14 to 0.91, $p < 0.05$
Consistency in results	Authors report data are consistent.
Precision in results	Precise, apart from tamoxefin comparison.
Directness of results	Some indirectness.

Explanation of acronyms

CI = confidence interval, CrI = credible interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[10];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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