Efficacy and safety of lamotrigine in the treatment of bipolar disorder across the lifespan: a systematic review

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Abstract

Background: Bipolar disorder (BD) is a cyclic mood disorder characterised by alternating episodes of mania/hypomania and depression interspersed with euthymic periods. Lamotrigine (LTG) demonstrated some mood improvement in patients treated for epilepsy, leading to clinical studies in patients with BD and its eventual introduction as maintenance therapy for the prevention of depressive relapse in euthymic patients. Most current clinical guidelines include LTG as a recommended treatment option for the maintenance phase in adult BD, consistent with its global licencing status.

Aims: To review the evidence for the efficacy and safety of LTG in the treatment of all phases of BD.

Methods: PubMed was searched for double-blind, randomised, placebo-controlled trials using the keywords: LTG, Lamictal, 'bipolar disorder', 'bipolar affective disorder', 'bipolar I', 'bipolar II', cyclothymia, mania, manic, depression, depressive, 'randomised controlled trial', 'randomised trial', RCT and 'placebo-controlled' and corresponding MeSH terms. Eligible articles published in English were reviewed.

Results: Thirteen studies were identified. The strongest evidence supports utility in the prevention of recurrence and relapse, particularly depressive relapse, in stabilised patients. Some evidence suggests efficacy in acute bipolar depression, but findings are inconsistent. There is little or no strong evidence in support of efficacy in acute mania, unipolar depression, or rapid-cycling BD. Few controlled trials have evaluated LTG in bipolar II or in paediatric patients. Indications for safety, tolerability and patient acceptability are relatively favourable, provided there is slow dose escalation to reduce the probability of skin rash.

Conclusion: On the balance of efficacy and tolerability, LTG might be considered a first-line drug for BD, except for acute manic episodes or where rapid symptom control is required. In terms of efficacy alone, however, the evidence favours other medications.

Keywords: bipolar disorder, cyclothymia, depression, lamotrigine, mania, mood stabilisation, rapid cycling

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Keypoints

1. Evidence from randomised, controlled trials suggests lamotrigine is effective in reducing the risk of depressive relapse in stabilised bipolar patients.
2. There is little or no evidence to support the efficacy of lamotrigine in acute mania or rapid-cycling bipolar disorder.
3. Lamotrigine has a favourable safety profile provided there is slow dose titration to reduce the risk of skin rash.

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Introduction

Bipolar disorder (BD) is an episodic mood disorder characterised by manic/hypomanic and depressive episodes interspersed with periods of euthymia.[1] The International Classification of Diseases – 10th Revision (ICD-10) includes separate diagnostic categories for mania (F30) and bipolar affective disorder (F31).[2] The diagnostic criteria for bipolar affective disorder require either a current or past episode of mania or hypomania in addition to at least one other affective episode. Diagnosis is subcategorised according to current affective episode (hypomanic, manic with or without psychotic symptoms, mild or moderate depression, severe depression with or without psychotic symptoms, mixed, or in remission). Starting from the publication of the *DSM*-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition), the American Psychiatric Association[3] has recognised two principal subtypes of BD: bipolar I (BD-I) and bipolar II (BD-II). In the current *DSM*-5, BD-I is characterised by mania and, although patients will often experience depressive episodes, depression is not required for a diagnosis. BD-II is characterised by hypomania and at least one depressive episode. In current classifications, including the *DSM*-5, a broader symptomatology is recognised, which includes cyclothymia (already classified as a distinct BD in earlier editions of the *DSM*), in which hypomanic episodes rapidly alternate with non-major depressive episodes, and 'other specified bipolar and related disorders'.[4] Cyclothymia is excluded from the classification of bipolar affective disorder in the ICD-10[5] but is included in the forthcoming ICD-11.[6]

Lifetime prevalence of BD-I and BD-II were estimated at 1.0% and 1.1%, respectively, in a large US population study undertaken between 2001 and 2003.[7] A more recent analysis as part of the World Health Organisation (WHO) World Mental Health Survey Initiative in 2011 cited aggregate lifetime prevalence figures of 0.6% for BD-I and 0.4% for BD-II based on data from an international sample of 61,392 participants.[8] With the inclusion of subsyndromal cases, the lifetime prevalence of any bipolar spectrum disorder may be as high as 6.5%.[9]

A greater allocation of health resources is required for adequate management of BD compared to unipolar depression and other chronic mental health conditions.[10] Psychiatric comorbidities, behavioural problems, substance abuse and eating disorders are common. The rate of attempted suicide in patients with BD, a particular risk in patients with depression, may be as high as 25%–50%.[10]

Lamotrigine (LTG) is a phenyltriazine-derived antiseizure medication (ASM), developed for the treatment of epilepsy during the 1980s.[11] Its mood effects were observed in early clinical trials during which some patients registered improvements in the 'happiness' and 'mastery' components of a health-related quality-of-life model.[12] Beginning in 1995, LTG entered a series of industry-sponsored clinical trials in patients to assess efficacy in all phases of BD. This led in 2003 to regulatory approval for relapse prevention in BD-I in the United States (US) and European Union (EU).[11,13]

LTG is currently licenced in more than 50 countries for depressive relapse in adults with predominantly depressive BD-I.[14,15] It is the only ASM licenced for depression and one of only three medications approved for depression in BD, the others being the antipsychotic quetiapine (QTP) and lithium (Li) (Table 1).

The mechanisms underpinning the therapeutic effect of LTG in BD remain unclear, in part reflecting a still incomplete understanding of the neurochemical and neurophysical irregularities underlying the disorder.[16] Antiseizure effects are thought to be mediated by modulation of calcium and voltage-sensitive sodium ion channels[17,18] and consequent inhibition of glutamate release which ultimately effects the suppression of supranormal neuronal activity.[18] Neuromodulatory effects may be of relevance in BD, in which dysregulation of neuronal excitability has been implicated.[18] A regulatory influence on serotonergic and glutamatergic signalling[18] may also contribute to antidepressive and neuroprotective effects.[19]

The primary aim of this review is to summarise the evidence from randomised, double-blind, placebo-controlled trials for the efficacy and safety of LTG in the treatment of all phases of BD. The efficacy findings from randomised trials with active comparators, meta-analyses and open-label studies are also discussed.

Methods

The review was guided by the PRISMA criteria for reporting systematic reviews. A literature

Table 1. Licenced indications in bipolar disorder for common mood-stabilising medications.

	Medication	BNF	EMA[a]	FDA
ASMs	Lamotrigine	Monotherapy or combination therapy for bipolar disorder in adults	Prevention of depressive episodes in adult patients (⩾18 years) with bipolar I disorder who experience predominantly depressive episodes Not indicated for acute treatment of manic or depressive episodes	Maintenance treatment of bipolar I disorder to delay time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy Treatment of acute manic or mixed episodes not recommended Effectiveness in acute treatment of mood episodes not established
	Carbamazepine	Prophylaxis of bipolar disorder in adult patients unresponsive to lithium Prophylaxis of bipolar disorder in paediatric patients	Prevention of manic–depressive psychosis in patients unresponsive to lithium	Treatment of acute manic and mixed episodes in bipolar I disorder
	Valproate	Treatment of manic episodes in adult patients	Treatment of manic episodes when lithium is contraindicated or not tolerated	Treatment of manic episodes
Antipsychotics	Aripiprazole	Treatment and recurrence prevention of mania in adult patients Treatment of mania in adolescent patients (13–17 years)	Treatment of moderate to severe manic episodes in bipolar I disorder in adults Prevention of manic episodes in adult patients with predominantly manic episodes who have previously responded to aripiprazole. Treatment for up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents (⩾13 years)	Acute treatment of manic and mixed episodes associated with bipolar I disorder
	Olanzapine	Monotherapy or combination therapy for mania in adult patients Prevention of recurrence in adult patients	Treatment of moderate to severe manic episodes in adult patients Prevention of manic recurrence in adults who have responded to an initial course of treatment	Acute treatment of manic or mixed episodes associated with bipolar I disorder Maintenance treatment of bipolar I disorder
	Quetiapine	Treatment of mania in adult patients Treatment of depression in adult patients Prevention of mania or depression in adult patients Treatment of mania in paediatric patients (12–17 years)	Treatment of moderate to severe manic episodes in adults (⩾18 years) Treatment of major depressive episodes in adults Prevention of recurrence of manic or depressed episodes in adult patients who have previously responded to quetiapine	Depressive episodes Manic episodes in bipolar I disorder

(continued)

Table 1. (continued)

	Medication	BNF	EMA[a]	FDA
	Risperidone	Treatment of mania in adult patients Short-term monotherapy for mania in paediatric patients (12–17 years)	Treatment of moderate to severe manic episodes in adult patients (⩾18 years).	Monotherapy or adjunctive therapy with lithium or valproate for treatment of acute mania or mixed episodes associated with bipolar I disorder
	Asenapine	Monotherapy or combination therapy of severe manic episodes in adult patients	Treatment of moderate to severe manic episodes associated with bipolar I disorder in adult patients	Acute monotherapy of manic or mixed episodes in adults and paediatric patients (10–17 years) Adjunctive treatment to lithium or valproate in adults Maintenance monotherapy in adults
	Lithium	Treatment and prophylaxis of bipolar disorder in adult patients Treatment and prophylaxis of bipolar disorder in paediatric patients (12–17 years).	Treatment of mania and hypomania Treatment of recurrent bipolar depression	Monotherapy of acute manic and mixed episodes in bipolar I disorder in patients 7 years and older Maintenance treatment in patients 7 years and older

ASMs, antiseizure medications; BNF, British National Formulary; EMA, European Medicines Agency; FDA, Food and Drug Administration.
[a]Information for some drugs taken from the UK electronic medicines compendium were not available from the EMA.

search strategy was formulated based on the PICOS framework (Population, Intervention, Comparator, Outcome and Study type). These variables were defined as follows:

P: Adult and paediatric patients with BD (BD-I, BD-II and BD-NOS) or cyclothymia.
I: Lamotrigine (Lamictal) monotherapy or adjunct therapy.
C: Placebo.
O: Efficacy, assessed either as a continuous variable (e.g., improvement in depression or mania rating scale scores) or as a dichotomous variable (e.g., response).
S: Double-blind, randomised, placebo-controlled trials.

Two authors independently searched the Medline/PubMed and Embase electronic databases without date restrictions in February 2020 and again in May 2021 using the keywords ('bipolar disorder' OR 'bipolar affective disorder' OR bipolar OR 'bipolar I' OR 'bipolar II' OR cyclothymia OR depression OR mania OR hypomania OR manic OR depressive) AND (lamotrigine OR Lamictal) AND ('randomised controlled trial' OR 'randomized controlled trial' OR 'randomised trial' OR 'randomized trial' OR 'controlled trial' OR RCT) AND (placebo OR placebo-controlled OR 'placebo controlled') and corresponding MeSH terms. Only studies with human participants and articles with full texts available in English were considered. Studies were eligible if they reported efficacy findings for LTG compared to placebo in paediatric or adult patients with any bipolar subtype and in any phase of the condition. Trials of LTG monotherapy and adjunct therapy were included. There were no additional restrictions on patient or study characteristics. The primary search was supplemented by hand-searching the references of relevant articles. Data were extracted to a custom form created in Microsoft Excel based on the Cochrane Collaboration data collection form for intervention reviews for randomised controlled trials (RCTs). Discrepancies were resolved by discussion between the authors. Efficacy data from studies with active comparator medications,

meta-analyses and open-label studies were also identified and included as supplementary evidence for efficacy and tolerability.

Risk of bias for eligible placebo-controlled RCTs was independently assessed by two authors using the Cochrane Collaboration Risk of Bias Tool. Disagreements were resolved by discussion between the authors and the final judgements determined by consensus.

Results

The PRISMA search flow diagram is shown in Figure 1. Of 2231 unique articles identified, 13 double-blind, randomised, placebo-controlled trials[14,20–31] met the criteria for inclusion. LTG monotherapy trials included two studies in patients with acute bipolar depression[20,23] and three relapse-prevention studies.[21,25,26] The relapse prevention trials included one trial in patients stabilised following a recent depressive episode,[26] one trial in patients stabilised following a recent manic/hypomanic episode,[25] and one trial in patients with rapid-cycling symptoms.[21] Adjunct LTG trials included five studies in patients with acute bipolar depression,[14,22,24,27,30] two studies in patients with rapid cycling,[28,30] and two relapse prevention studies.[29,31] Four studies included only BD-I patients,[20,25,26,31] one study included only BD-II patients,[24] and the other eight studies included both BD-I and BD-II patie nts.[14,21–23,27–30] Of these eight studies, only two reported findings for BD-I and BD-II patients separately.[21,30] One monotherapy trial[23] and two adjunct trials[22,24] in patients with acute depression included mixed samples of patients with bipolar and unipolar depression. One study was in patients with rapid-cycling BD-I or BD-II and a recent substance use disorder.[28] All studies were in adult samples except for one relapse prevention trial of adjunct LTG, which included only paediatric patients.[31] Trial duration ranged from 6 to 12 weeks for acute trials and from 6 to 18 months for relapse prevention trials. Sample size ranged from 23 participants to 463 participants. In total, 873 patients were randomised to LTG. Efficacy data were available for 841 of these patients (van der Loos et al.[29] reported long-term follow-up data for 30 out of the 64 patients who were randomised to LTG in the initial study phase reported by van der Loos *et al.*[27] These patients have only been counted once). LTG dosage at trial endpoint was 50–500 mg/day. Existing bipolar medication in add-on trials included paroxetine, fluoxetine, Li, divalproex, and QTP.

In addition to the double-blind, randomised, placebo-controlled trials, five blinded (double or single) randomised trials comparing LTG to an active comparator medication were identified. Four of these studies were in patients with acute depression[32–35] and compared LTG with olanzapine/fluoxetine combination (OFC) ($n=2$), Li ($n=1$) and citalopram ($n=1$). The studies comparing LTG to OFC and Li were monotherapy trials. The study comparing LTG with citalopram was an adjunct treatment trial in patients already treated with a first-line mood stabiliser.[35] The fifth randomised trial with an active comparator was a double-blind monotherapy trial in patients with acute mania in which LTG was compared with Li.[36]

Eighteen open-label studies were identified; four relapse/recurrence prevention studies, nine acute depression studies, and five acute mania/hypomania studies.

Risk of bias

The Cochrane risk of bias assessment resulted in an AHRQ (Agency for Healthcare Research and Quality) rating of Good for three studies, Fair for three studies and Poor for seven studies. Judgements for individual items of the risk of bias assessment for each study are available in the supplementary material. Most studies were judged as having a low risk of bias for randomisation, blinding and selective reporting. However, more than half of the studies were considered to present an unclear or high risk of bias for incomplete outcome data, frequently due to relatively high dropout rates. Other potential sources of bias were identified for all studies, but in most cases, it was considered that there was insufficient evidence to assess the degree to which these problems might introduce additional bias, and as a result, the majority of studies were judged as having unclear risk for this item.

Efficacy

Prevention of relapse/recurrence. Table 2 shows a summary of study characteristics for the RCTs and open-label studies of LTG for prevention of relapse/recurrence reviewed in this section.

Randomised, controlled studies. The efficacy of LTG monotherapy in preventing relapse in

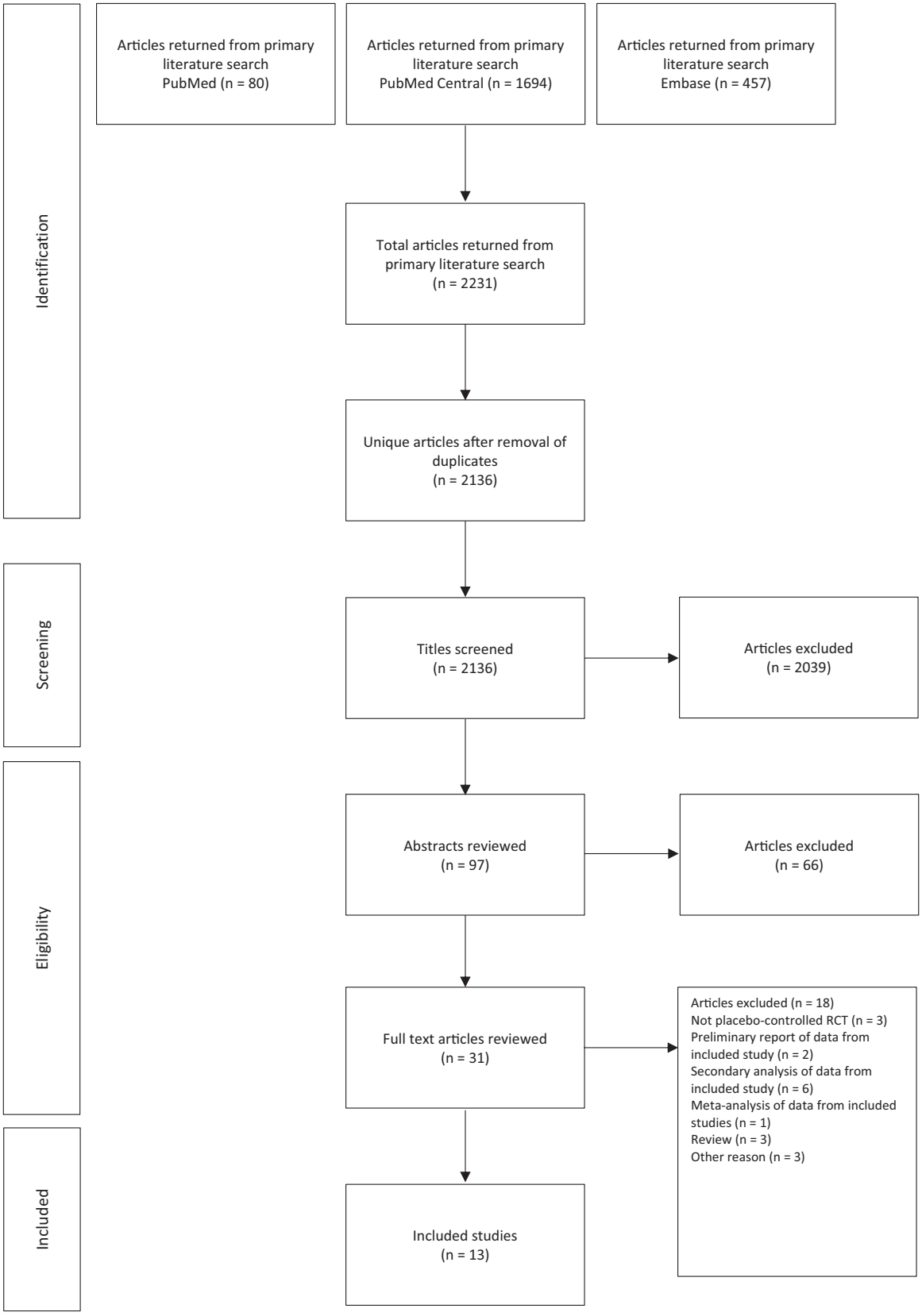

Figure 1. PRISMA search diagram.

Table 2. Summary of relapse/recurrence prevention studies.

Study	Type	Bipolar subtype	Monotherapy or adjunct	Comparator	*N*	Duration	LTG dose (mg/d)
Calabrese *et al.*[21,a]	Randomised, double-blind, flexible-dose, parallel-group, placebo-controlled, multi-centre study	Rapid-cycling BD-I; BD-II	Monotherapy	Placebo	182	26 weeks	100–300
Bowden *et al.*[25,a]	Randomised, double-blind, parallel-group, placebo-controlled, multi-centre study	BD-I	Monotherapy	Li; placebo	175	18 months	100–400
Calabrese *et al.*[26,a]	Randomised, double-blind, parallel-group, placebo-controlled, multi-centre study	BD-I	Monotherapy	Li; placebo	463	18 months	50; 200; 400
van der Loos *et al.*[29]	Randomised, double-blind, placebo-controlled trial	BD-I; BD-II	Adjunct	Placebo	55	60 weeks	200
Findling *et al.*[31]	Randomised, double-blind, parallel-group, placebo-controlled, multi-centre withdrawal study	BD-I	Adjunct	Placebo	173	36 weeks	[b]
Licht *et al.*[37]	Randomised, open-label study	BD-I	Monotherapy[c]	Li	155	⩽5.8 years	379 ± 66[d]
Pavuluri *et al.*[38]	Open-label, prospective study (paediatric patients)	BD-I; BD-II	Monotherapy	NA	46	6 weeks	150; 200[e]
Pan *et al.*[39]	Open, parallel-group, naturalistic observation study	BD-I; BD-II	Either	OLZ	51	12 months	86.5 ± 49.6[d]
Terao *et al.*[40]	Post-marketing surveillance study	BD-I; BD-II; BD-NOS	Either	NA	989	12 months	200[f]

BD, bipolar disorder; CBZ, carbamazepine; Li, lithium; LTG, lamotrigine; NA, not applicable; NOS, not otherwise specified; OLZ, olanzapine; VPA, sodium valproate.
[a]Placebo-controlled study included in one or more meta-analysis.
[b]Dose dependent on co-medication (valproate or carbamazepine) or monotherapy.
[c]Co-medication permitted during the first 6 months of treatment.
[d]Mean ± standard deviation.
[e]Dose dependent on body weight: 150 mg/day (⩽30 kg); 200 mg/day (>30 kg).
[f]Dose as per prescribing information. Target dose with VPA 100 mg/day. Target dose with CBZ 300 mg/d.

stabilised adult patients with BD-I was investigated in two industry-sponsored 18-month, multicentre, RCTs in which LTG monotherapy was compared with Li monotherapy and placebo.[25,26] Samples were 'enriched' to include only patients who both tolerated LTG and demonstrated mood stability during a 8- to 16-week pre-randomisation open-label phase, which included at least 1 week of LTG monotherapy. All other psychotropic medications were discontinued. The primary efficacy endpoint in each study was time to intervention (either additional pharmacotherapy or electroconvulsive therapy) for any mood episode.

In the first study,[25] 175/349 patients, who were stabilised following a manic/hypomanic episode with open-label LTG, were randomised. Patient characteristics at baseline were consistent with at least moderately severe illness. LTG doses were adjusted between 100 and 400 mg/day depending on clinical response. Over the follow-up period, LTG was significantly superior to placebo in prolonging time to intervention for any mood episode ($p = 0.02$) and time to intervention for a depressive episode ($p = 0.02$). There was no difference between LTG and Li in either time to intervention for any mood episode ($p = 0.46$), or time to intervention for a depressive episode ($p = 0.36$). For time to intervention for manic/hypomanic or mixed episodes, LTG did not separate from placebo ($p = 0.28$), and there was a non-significant trend favouring Li over LTG ($p = 0.09$). Among patients treated with LTG, 28 mood episodes requiring intervention were reported, of which 20 were manic/hypomanic or mixed states and eight were depressive episodes. The most frequent AEs leading to withdrawal in the open-label phase were rash ($n = 17$; 5%) and mania ($n = 12$; 3%). In the randomised phase, two patients (3%) in the LTG group discontinued due to mania but there were no withdrawals due to rash.

In the second study,[26] 463 patients were randomised to LTG (50, 200 or 400 mg/day), Li or placebo, having been stabilised on LTG adjunct or monotherapy during a 8- to 16-week open-label phase following a major depressive episode. Sixty-one percent of patients had required previous psychiatric hospital admission, and 35% had a history of at least one previous suicide attempt. The primary efficacy analysis was based on combined data from the LTG 200 and 400 mg/day groups, excluding data from the LTG 50 mg/day group. During the randomised monotherapy phase, the median (95% confidence interval (CI)) time to intervention for any mood episode was 93 (58–180) days for placebo, 170 (105 to not evaluable ('not evaluable' due to insufficient data)) days for Li and 200 (146–399) days for LTG. LTG (combined data for 200 and 400 mg/day) was superior to placebo for time to intervention for any mood episode ($p = 0.029$). There was no difference between LTG and Li. Interventions for depression were more frequent than interventions for mania by a ratio of 3:1. Kaplan–Meier survival analysis was used to estimate freedom from intervention for depression and mania due to insufficient numbers of events in some treatment groups. Kaplan–Meier estimates for freedom from intervention for depression at 1 year were 57%, 46% and 45% for LTG, Li and placebo, respectively, and for freedom from intervention for mania at 1 year 77%, 86% and 72% for LTG, Li and placebo, respectively. Based on this analysis, LTG was superior to placebo for time to intervention for depressive episodes ($p = 0.047$). There was no difference between LTG and placebo ($p = 0.339$) or between Li and LTG ($p = 0.125$) in time to intervention for mania. When LTG groups were analysed separately, LTG 200 mg/day was superior to placebo for time to intervention for any mood episode ($p = 0.013$) and time to intervention for depression ($p = 0.028$) but not for time to intervention for mania. Analysed separately, the 50 and 400 mg/day LTG groups were not superior to placebo on any of these measures. A later analysis of the data from this study[41] showed switch-to-mania was no more frequent with LTG than placebo during the first 6 months. The most common AEs leading to discontinuation during the open-label phase were rash ($n = 38$; 4%), mania ($n = 10$; 1%) and depression ($n = 10$; 1%). During the randomised phase, rash led to the withdrawal of 4% (nine patients) in the LTG groups. Four suicides were reported, two during the open-label phase, one during the randomised phase in a patient taking LTG 400 mg/day, and one 3 weeks after discontinuation from the open-label phase.

A meta-analysis of the pooled data from the two RCTs[42] consolidated most of the initial findings, but indicated significantly longer time-to-intervention for mania/hypomania or mixed episodes with LTG compared to placebo ($p = 0.034$). A second meta-analysis, which excluded patients who relapsed within 90 days,[43] found time-to-intervention for any mood episode remained significantly greater for LTG than placebo ($p = 0.002$).

Two more recent studies have provided evidence of efficacy for relapse prevention for adjunct LTG. Findling *et al.*[31] conducted a placebo-controlled withdrawal trial in 173 paediatric BD-I patients. Time-to-occurrence of a bipolar event (TOBE), the primary outcome, was monitored up to 36 weeks after an initial 18-week open-label phase during which LTG was added to existing treatment comprising one or two mood stabilisers and/or antipsychotics. Patients were at least moderately ill (baseline CGI-BP ≥ 4). Efficacy analysis was based on the intention-to-treat (ITT) population. In phase I, the mean (standard error, SE) time to stabilisation was 101 (1.6) days. In the randomised withdrawal phase, the mean (SE) TOBE for patients with depressive, manic/hypomanic and mixed state index episodes, respectively, were: LTG 155 (14.7) days, placebo 50 (3.8) days; LTG 163 (12.2) days, placebo 120 (12.2) days; and LTG 136 (15.4) days, placebo 107 (13.8) days. For the overall population, the difference between LTG and placebo for TOBE was not statistically significant based on stratified log-rank analysis (hazard ratio, HR = 0.63; 95% CI = 0.38–1.03; $p = 0.072$). However, Cox regression analysis which controlled for index mood state, the use of antipsychotic medication, the use of ADHD medication, age and sex, revealed a significantly greater treatment effect for LTG *versus* placebo ($\chi^2 = 3.9$; $p = 0.047$). In addition, a stratified log-rank analysis of TOBE significantly favoured LTG in the subgroup of patients aged 13–17 years (HR = 0.46; 95% CI = 0.24–0.88; $p = 0.015$), but not younger patients (HR = 0.93; 95% CI = 0.42–2.10; $p = 0.877$), and for patients not taking ADHD medication ($p = 0.035$), but not those who were taking ADHD medication. Dermatological adverse events (AEs) were reported in 4% of patients in the open-label phase and 2% in the randomised phases.

A long-term follow-up of an earlier placebo-controlled RCT in patients with either BD-I or BD-II and acute depression (see below)[27] enrolled 55 responders in a 60-week extension phase to compare time to relapse between groups treated with Li and either adjunct LTG or adjunct placebo.[29] After the initial 8-week study, open-label paroxetine was added for an additional 8 weeks in patients who had not responded in the initial randomised phase. During the extension phase, patients who responded in either of the previous phases were retained in the trial until relapse or recurrence of a depressive or manic episode. The response seen with LTG with or without paroxetine during the initial phases based on Clinical Global Impression-Bipolar Version (CGI-BP) scores was reported to have been maintained during the follow-up period. The median time to relapse or recurrence, defined as loss of initial response based on Montgomery-Åsberg Depression Rating Scale (MADRS) scores ($\geq$50% decrease in baseline MADRS), was greater for LTG (10 months; 95% CI = 1.1–18.8) than placebo (3.5 months; 95% CI = 0.7–7.0). No formal statistical analysis of these results was possible, however, due to the selected group for follow-up.

In addition to these studies, two industry-sponsored pre-licencing RCTs in rapid-cycling patients have been conducted, only one of which was subsequently published.[21] The study featured an enriched sample of 182 patients with either BD-I (71%) or BD-II who met stabilisation criteria following open-label treatment with LTG. These patients were subsequently randomised to continue treatment with LTG monotherapy or placebo after tapered withdrawal of existing co-medication. Dose could be adjusted between 100 and 500 mg/day according to individual patient requirements. The primary outcome was time to additional pharmacotherapy for emerging symptoms. Efficacy data were analysed based on the ITT population. Over 6 months, time-to-intervention did not differ significantly between LTG and placebo groups ($p = 0.177$), although patients taking LTG had significantly longer survival-in-study times which account for any premature discontinuation ($p = 0.036$). Median survival time was 6 weeks longer with LTG than placebo (18 weeks *vs* 12 weeks). The proportion of patients who remained stable without relapse at 6 months was also significantly greater for LTG (41% *vs* 26%; $p = 0.03$). Secondary analysis showed a larger treatment effect in BD-II than BD-I patients with a trend towards significantly longer time-to-intervention for LTG than placebo ($p = 0.073$) and a significant difference between LTG and placebo for survival in study in BD-II ($p = 0.015$). Eighty percentage of patients requiring additional medication were treated for depressive symptoms.

Full efficacy data for placebo-controlled RCTs are available in the online supplementary material.

Meta-analyses. A meta-analysis[44] which included the three industry-sponsored RCTs summarised in this section reported risk ratios (RRs) of less than one for LTG compared to placebo for

relapse for any mood episode (RR = 0.83; 95% CI = 0.68–1.00; $p = 0.047$), relapse for manic/mixed episodes (RR = 0.96; 0.68–1.34; $p = 0.800$) and relapse for depressive episodes (RR = 0.70; 95% CI = 0.36–1.36; $p = 0.290$). However, the 95% CI for one of the two studies in the analysis of depressive relapse[26] and for the pooled data for depressive relapse extended beyond one. Similarly, for manic/mixed relapse, only one of the two included studies had an RR less than 1[25] and both studies had wide confidence intervals extending beyond 1. These results were reflected in the p values for manic/mixed and depressive relapse which did not reach statistical significance and led the authors to conclude that the data did not support LTG monotherapy for either indication.

More recently, Oya *et al.*[45] aggregated data from double-blind, placebo-controlled RCTs of relapse prevention in stabilised patients receiving LTG or Li either as monotherapy or as adjuncts to existing treatment. Findings from four studies of LTG, which included three of the studies individually summarised above and one additional Japanese study, and two studies of Li found statistically greater efficacy for both drugs compared with placebo for prevention of mood episodes (LTG: RR = 0.81, 95% CI = 0.70–0.93; $p = 0.004$; $I^2 = 0\%$, number needed to treat (NNT) = 8.3, 95% CI = 5.0–25.0; Li: RR = 0.52, 95% CI = 0.41–0.66; $p < 0.00001$; $I^2 = 0\%$; NNT = 2.3, 95% CI = 1.6–4.2) and superiority with regard to all-cause discontinuation (LTG: RR = 0.89, 95% CI = 0.81–0.98, $p = 0.02$, $I^2 = 52\%$, number needed to harm (NNH) = 11.1, 95% CI = 7.1–25.0; Li: RR = 0.57, 95% CI = 0.47–0.69, $p < 0.00001$, $I^2 = 0\%$, NNH = 2.3, 95% CI = 1.6–4.3). Although no direct comparison between the drugs was performed, Li appeared to be superior to LTG for preventing relapse.

The relative antimanic/antidepressive efficacies of LTG and other medications used in bipolar maintenance therapy were compared in an analysis by Popovic *et al.*[46] A polarity index (PI), corresponding to the ratio between the NNT for prevention of depression and the NNT for the prevention of mania was calculated for each medication, with a PI > 1 denoting a greater relative antimanic effect and a PI < 1 denoting a greater relative antidepressant effect. Analysis of data from RCTs resulted in a PI of 0.40 for LTG, suggesting greater efficacy in depression. Indices reported for other drugs were as follows: risperidone 12.09; aripiprazole 4.38; ziprasidone 3.91; olanzapine (OLA) 2.98; Li 1.39; and QTP 1.14.

Open-label studies. A randomised open-label study in BD-I patients found no significant differences between LTG and Li in time-to-recurrence or relapse over periods of up to 5 years. The RRs for LTG *versus* Li for recurrence or relapse for any mood episode, manic episodes and depressive episodes were 0.92, 1.91 and 0.69, respectively, indicating greater relative efficacy for LTG in preventing depressive relapse and for Li in preventing manic relapse.[37]

A long-term enriched, naturalistic study in 46 patients stabilised on either LTG or OLA[39] reported a significantly lower recurrence rate for depressive episodes with OLA ($p = 0.010$). Recurrence rates were not significantly different between groups for any mood episode (OLA 35.0%; LTG 57.7%; $p = 0.127$) or for manic episodes (OLA 15.0%; LTG 0%; $p = 0.075$). Similarly, time-to-recurrence for depressive episodes significantly favoured OLA ($p = 0.033$), but time-to-recurrence for any mood episode was not significantly different between groups ($p = 0.195$). More patients taking LTG required co-administration of antidepressants than patients taking OLA ($p = 0.008$). The relatively small sample size in this study may have limited the statistical power to detect differences between treatments.

A post-marketing surveillance study conducted in Japan[40] reported relapse/recurrence rates and time to relapse/recurrence in 966 patients over a 12-month period. Of the 703 patients with complete data, 466 (66.3%) experienced no episodes of recurrence or relapse. The 25th percentile for time to relapse/recurrence in the remaining patients was 105 days for any mood episode, 274 days for depressive episodes and 259 days for manic/hypomanic or mixed episodes. The rate of recurrence or relapse was 20% for both manic and depressive episodes. Remission from depressive symptoms based on the Hamilton Depression Rating Scale (HAM-D) increased from 21.1% at treatment initiation to 67.4% after 10–12 months, based on data from 536 patients who remained in the study. Remission from manic symptoms based on the Young Mania Rating Scale (YMRS) was 91.0% at treatment initiation and 97.3% after 10–12 months in 514 patients with available data. The stability of YMRS over time was interpreted as an indication that LTG was effective at stabilising mood in the long term.

There are few data on relapse prevention with LTG in paediatric samples. A single open-label study[38] in 46 paediatric BD-I and BD-II patients initially stabilised with second-generation antipsychotics reported a sustained response from Week 8, when antipsychotics were withdrawn, to Week 14 after 6 weeks of LTG monotherapy. Response rates at Week 14 were 72% for manic symptoms (based on YMRS) and 82% for depressive symptoms (based on the Children's Depression Rating Scale-Revised (CDRS-R)), suggesting bimodal efficacy in maintaining symptom control. The overall remission rate at Week 14 was 56%. Three patients (23%) in remission at Week 8 had relapsed by Week 14. Mean CDRS-R scores continued to decline during the LTG monotherapy phase (between Weeks 8 and 14) and were significantly lower at Week 14 than Week 8 ($p < 0.05$). During the LTG titration phase up to Week 8, significant reductions from baseline were observed in YMRS ($p < 0.001$), CDRS-*R* ($p < 0.001$), Child Mania Rating Scale – Parent ($p < 0.001$), and in CGI-BP Overall, CGI-BP Mania and CGI-BP Depression scores as well as Overt Aggression Scale (OAS) Aggression and Irritability scores (all $p < 0.01$). Most AEs were mild or moderate. Rash, considered 'benign', was reported in three patients (6.4%) and led to treatment withdrawal as a precautionary measure.

Most of the data on relapse prevention comes from patients with BD-I. The efficacy of LTG for the prevention of relapse in BD-II is still largely unclear[47]; only two of the RCTs summarised above included patients with BD-II, one of which was in patients with rapid-cycling symptoms.

Acute depression. Table 3 shows a summary of study characteristics for the RCTs and open-label studies of LTG for acute depression reviewed in this section.

Randomised controlled studies. The first pre-licencing phase III study to report findings was a multi-centre dose comparison in adult BD-I patients with current major depression.[20] One hundred ninety-five patients were randomised to monotherapy with LTG 50 mg/day, LTG 200 mg/day or placebo for 7 weeks. The primary outcome was change in baseline scores on the 17-item HAM-D (HAM-D_{17}). Sample characteristics at time of enrolment suggested moderately to markedly severe illness. Patients in both LTG groups demonstrated significant improvement ($p < 0.05$) in observed HAM-D_{17} scores but not for last observation carried forward (LOCF) scores, although the 200 mg/day group demonstrated a trend towards improvement ($p = 0.84$). Significant improvements in secondary outcomes (observed and LOCF HAM-D item 1 (depressed mood), MADRS, CGI-Severity (CGI-S) and CGI-Improvement (CGI-I)) were reported for LTG 200 mg/day (all $p < 0.05$). LTG 50 mg/day demonstrated statistically significant improvement in observed HAM-D_{17}, MADRS, CGI-S, CGI-I and MRS, and in observed and LOCF HAM-D item 1 (all $p < 0.05$). Significant improvements in observed HAM-D_{17} scores were seen within 5 weeks (LTG 200 mg/day only) and in observed and LOCF HAM-D item 1 scores within 3 weeks (both LTG groups at 50 mg/day (The LTG 200 mg/day group was titrated to 50 mg/day at Week 3)). Both LTG groups showed a mean 13-point improvement in HAM-D_{17} observed scores (both $p < 0.05$ *vs* placebo). Response rates at Week 7 were 52%, 41% and 26% for LTG 200 mg/day, LTG 50 mg/day and placebo, respectively. Although LTG was significantly better than placebo on secondary outcomes, LOCF scores for the primary outcome were not significantly improved with either dose. Rash led to withdrawal in seven patients (5%) receiving LTG, three patients in the 50 mg/day group and four patients in the 200 mg/day group. Other AEs resulting in withdrawal in the LTG groups included worsening psychiatric depression (50 mg/day, $n = 3$; 5%), suicidal ideation (50 mg/day, $n = 1$; 2%, 200 mg/day, $n = 1$; 2%), suicide attempt (50 mg/day, $n = 1$; 2%) and mania (200 mg/day $n = 2$; 3%).

Four further pre-licencing RCTs in acute bipolar depression were conducted. The results of these studies were not published individually, but the results have been included in meta-analyses pooling data from all five studies. None of the studies individually found significantly greater improvement in primary outcomes for acute depressive symptoms than with placebo.[58]

A contemporary crossover study compared LTG and gabapentin (GBP) monotherapies and placebo in patients with treatment refractory bipolar or unipolar affective disorders, the majority with rapid-cycling symptoms.[23,48] Findings from a subgroup of 31 patients (BD-I $n = 11$; BD-II $n = 14$; unipolar $n = 6$) with evaluable data for all three treatments[48] reported response rates (CGI-BP rating of 'much improved' or 'very much improved') after 6 weeks of 52%, 26% and 23% for LTG, GBP and placebo, respectively.

Table 3. Summary of acute depression studies.

Study	Type	Bipolar subtype	Monotherapy or adjunct	Comparator	*N*	Duration	LTG dose (mg/d)
Calabrese *et al.*[20,a]	Randomised, double-blind, parallel-group, placebo-controlled, multi-centre study	BD-I	Monotherapy	Placebo	195	7 weeks	50; 200
Frye *et al.*[48,b]	Randomised, double-blind, crossover study	BD-I; BD-II; Rapid-cycling	Monotherapy	GBP; placebo	38	6 weeks[c]	300–500
Obrocea *et al.*[23,b]	Randomised, double-blind, crossover study	BD-I; BD-II; Rapid-cycling	Monotherapy	GBP; placebo	45	6 weeks[c]	300–500
Brown *et al.*[32,d]	Randomised, double-blind study	BD-I	Monotherapy	OFC	410	7 weeks	200
Brown *et al.*[33,d]	Randomised, double-blind study	BD-I	Monotherapy	OFC	410	25 weeks	200
Suppes *et al.*[34]	Randomised, single-blind, study	BD-II	Monotherapy	Li	102	16 weeks	200
Normann *et al.*[22]	Randomised, double-blind, parallel-group, placebo-controlled study	BD-I; BD-II	Adjunct (PAR)	Placebo	40	9 weeks	200
Barbosa *et al.*[24]	Randomised, double-blind, placebo-controlled study	BD-II	Adjunct (FXT)	Placebo	23	6 weeks	100
van der Loos *et al.*[27,a]	Randomised, double-blind, placebo-controlled, multi-centre study	BD-I; BD-II	Adjunct (Li)	Placebo	124	8 weeks	200
Wang *et al.*[28]	Randomised, double-blind, placebo-controlled, pilot study	BD-I; BD-I	Adjunct (Li + DVX)	Placebo	36	12 weeks	150–200
Geddes *et al.*[14]	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre, 2 × 2 factorial trial	BD-I; BD-II	Adjunct (QTP)	Placebo	202	12 weeks	200[e]
Kemp *et al.*[30]	Randomised, double-blind, placebo-controlled study	Rapid-cycling BD-I; BD-II[f]	Adjunct (Li + DVX)	Placebo	49	12 weeks	150–200
Schaffer *et al.*[35]	Randomised, double-blind, pilot study	BD-I; BD-II	Adjunct	CTP	20	12 weeks	—
Nierenberg *et al.*[49]	Randomised, open-label study	BD-I; BD-II	Adjunct (AD)	Inositol; RIS	66	16 weeks	150–250
Nolen *et al.*[50]	Randomised, open-label study	BD-I; BD-II	Adjunct (Li; VPA; CBZ)	TCP	20	10 weeks	25–400
Calabrese *et al.*[51]	Open-label, prospective, multi-centre trial	BD-I; BD-II; BD-NOS	Either	NA	75	48 weeks	50–500

(continued)

Table 3. (continued)

Study	Type	Bipolar subtype	Monotherapy or adjunct	Comparator	*N*	Duration	LTG dose (mg/d)
Bowden *et al.*[52]	Open-label, multi-centre trial	BD-I; BD-II; Rapid-cycling	Either	NA	75	48 weeks	100–500
McElroy *et al.*[53]	Open-label extension to Calabrese *et al.*[20]	BD-I	Either	NA		52 weeks	50–200
Chang *et al.*[54]	Open-label study (paediatric patients)	BD-I; BD-II; BD-NOS	Either	NA	20	8 weeks	100–200[g]
Chang *et al.*[55]	Open-label, prospective study	BD-II	Adjunct	NA	109	52 weeks	—
Watanabe *et al.*[56]	Open-label, observational study	BD-I; BD-II; BD-NOS	Either (SSRI; SNRI; TC: AP)	NA	445	12 months	5–400
Born *et al.*[57]	Open-label, retrospective, prospective study	BD-I; BD-II; Rapid-cycling	Either (Li; CBZ; VPA; TPM)	NA	20	⩽24 months	100–500

AD, antidepressant; AP, antipsychotic; BD, bipolar disorder; CBZ, carbamazepine; CTP, citalopram; DVX, divalproex; FXT, fluoxetine; GBP, gabapentin; Li, lithium; LTG, lamotrigine; NA, not applicable; NOS, not otherwise specified; OFC, olanzapine fluoxetine combination; PAR, paroxetine; QTP, quetiapine; RIS, risperidone; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TC, tricyclic antidepressant; TCP, tranylcypromine; TPM, topiramate; VPA, sodium valproate.
[a]Placebo-controlled study included in one or more meta-analysis.
[b]Obrocea and Frye include overlapping patient data. Obrocea provided data for an expanded patient sample.
[c]Double crossover with three 6-week treatment periods.
[d]Initial and extension phases of same study. Brown *et al.*[33] includes initial 7-week period reported by Brown *et al.*[32]
[e]200 mg/day with concurrent VPA. 400 mg/day with concurrent combined oral contraceptives.
[f]Included patients with acute mania/hypomania, mixed episodes or depression.
[g]50–100 mg/day with concurrent VPA.

Post hoc analysis showed significantly greater response for LTG *versus* placebo ($p=0.022$) and GBP ($p=0.011$). Analysis by index affective episode showed non-significant trends in between-group differences, with a higher response rate with LTG than GBP or placebo for both acute mania (LTG 44%; GBP 20%; placebo 32%; $p=0.165$) and acute depression (LTG 45%; GBP 26%; placebo 19%; $p=0.065$). The results from an expanded sample of 45 patients, who received treatment with at least one medication[23] were consistent with the earlier findings. In the total sample of patients exposed to any treatment, LTG was more effective than either GBP or placebo with response rates of 51%, 28% and 21%, respectively, after 6 weeks. Response rates for the 36 patients who completed all three phases of the study showed a similar pattern (LTG 53%, GBP 28% and placebo 22%; $p=0.01$). Results for BD were not reported separately; however, a significant relationship between LTG response and diagnosis of BD was reported (Pearson's $r=-0.32$; $p=0.049$). Other factors associated with response with LTG included male gender ($r=0.37$; $p=0.22$), exposure to fewer medication trials ($r=-0.40$; $p=0.015$) and a history of fewer hospitalisations ($r=-0.32$; $p=0.050$); of these variables, only number of trials and male gender were independent predictors of response. One patient developed rash after 15 weeks during continuation of treatment with LTG which developed into toxic epidermal necrolysis (TEN).

Controlled trials with active comparators include a 7-week double-blind RCT comparing LTG and OFC in patients with acute BD-I depression, which reported significantly greater improvement with OFC in CGI-S ($p=0.002$, effect size = 0.26), MADRS ($p=0.002$, effect size = 0.24) and YMRS ($p=0.001$, effect size = 0.24). Response (⩾50% reduction in MADRS) was not significantly different between groups (OFC 68.8%; LTG 59.7%; $p=0.073$), but mean time to response was significantly lower for OFC ($p=0.01$), probably as a result of the need for more gradual titration with LTG. Overall, response and remission rates

were similar between groups. The incidence of suicidal and self-injurious behaviour significantly favoured OFC (OFC 0.5%; LTG 3.4%, $p = 0.037$).[32] A follow-up[33] over 25 weeks continued to show significantly greater improvement in CGI-S ($p = 0.008$), MADRS ($p = 0.005$) and YMRS ($p < 0.001$) with OFC. There were no significant differences between the LTG and OFC treatment groups in rate of depressive relapse (MADRS > 15) in patients in remission after 7 weeks ($p = 0.528$), or in treatment-emergent mania ($p = 0.401$).

A 16-week randomised single-blind trial comparing LTG and Li in 98 patients with acute BD-II depression, 72% with rapid-cycling symptoms[34] reported significant decreases from baseline in HAM-D_{17}, the primary outcome (LTG and Li both $p < 0.0001$), MADRS (LTG and Li both $p < 0.001$) and YMRS (LTG and Li both $p < 0.001$). There were no differences between drugs on any measure. More than 65% of patients taking LTG met HAM-D_{17} criteria for both response and remission, compared to 55% taking Li. There were no significant differences in response between patients with and without rapid-cycling symptoms.

In addition to the monotherapy trials summarised above, several studies have reported findings from studies of adjunct LTG in patients with depression who were unresponsive to existing treatment. Samples often included patients with unipolar depression. The earliest of these enrolled 40 patients with BD-I ($n = 4$), BD-II ($n = 3$) or unipolar depression who were currently treated with paroxetine and were randomised to receive either adjunct LTG or adjunct placebo.[22] Sample characteristics suggested patients were moderately to markedly ill. The primary efficacy outcome was change in baseline HAM-D. Analysis of efficacy was based on data from the ITT population. After 9 weeks, scores were significantly reduced in both adjunct LTG and adjunct placebo groups ($p < 0.0001$) with no difference between groups. There were no differences between LTG and placebo in response rate (≥50% reduction in baseline total HAM-D, LTG 55% and placebo 50%) or in time to response. When analysed separately, improvements in most individual HAM-D items showed no between-group differences. Only items 1 (depressed mood), 2 (guilt feelings), and 7 (work and interest) showed significantly greater improvement with LTG ($p = 0.0019$, $p = 0.0011$ and $p = 0.049$, respectively). This study included only a small number of patients with BD, and the results for these patients were not reported separately. However, subgroup analysis of the primary outcome suggested bipolarity did not significantly influence treatment efficacy.

Barbosa *et al.*[24] reported findings for 23 adult patients with BD-II ($n = 8$) or unipolar major depression ($n = 15$) who had been treated unsuccessfully with fluoxetine monotherapy and were randomised to receive either adjunct LTG or placebo. After 6 weeks, LTG was associated with a significantly greater improvement than placebo in CGI-S scores ($p = 0.03$) and significantly greater response defined as a CGI-I rating of ≤2 (LTG 84.62%;placebo 30.00%; $p = 0.013$). Improvements in HAM-D and MADRS scores, the primary outcome measures, showed no differences between LTG and placebo, but in light of the small sample size it is possible that this result could be explained by the limited statistical power of the study. There were no differences in improvement between patients with BD or unipolar depression on any of the efficacy outcomes. One patient receiving LTG who had no history of BD was withdrawn from the study due to a hypomanic episode.

van der Loos *et al.*[27] reported findings from a study of adjunct LTG compared with adjunct placebo in 124 Li-treated patients with BD-I or BD-II and current major depression. Enrolled patients had a MADRS score of ≥18 and a CGI-BP severity score of ≥4, indicating moderate severity of illness. Efficacy analysis was based on ITT. After 8 weeks, the mean decrease in MADRS scores was significantly greater for LTG than placebo ($p = 0.024$). Response rate (≥50% reduction in MADRS total score) was also significantly greater for LTG (LTG 51.6%; placebo 31.7%; $p = 0.030$). Response based on improvement in CGI-BP was not greater than placebo, however (LTG 64.1%; placebo 49.2%; $p = 0.105$). Switch to mania/hypomania was reported in five patients (7.8%) with LTG, four of whom had rapid-cycling, and two patients (3.3%) taking placebo ($p = 0.441$).

Wang *et al.*[28] evaluated adjunct LTG against adjunct placebo in 36 patients aged 16–65 years with rapid-cycling BD-I or BD-II and recent substance use disorder who had not met criteria for bimodal response (MADRS ≤ 19, YMRS ≤ 12 and Global Assessment of Functioning (GAF) ≥ 51 sustained for 4 weeks) following 16 weeks open-label treatment with a combination of Li and

divalproex. Analysis of efficacy data was based on the ITT population. After 9 weeks, patients treated with adjunct LTG did not show greater improvements in either MADRS or YMRS total scores than patients treated with adjunct placebo based on analysis of covariance (ANCOVA) with baseline scores as the covariate ($p=0.27$ and $p=0.25$, respectively). Response rates did not differ between groups (LTG 39%; PLB 33%; $p=1.00$) and rates of remission (28%) and bimodal response (44%) were the same in each group. Only 16 patients, eight in each treatment arm, completed the study with most discontinuations due to lack of efficacy. Baseline clinical characteristics indicated a high rate of comorbid anxiety disorder (72% in the LTG group and 67% in the placebo group), psychosis (LTG 56%, placebo 44%), previous suicide attempt (LTG 39%, placebo 28%) and hospitalisation (LTG 72%, placebo 44%).

The CEQUEL (Comparative Evaluation of Quetiapine plus Lamotrigine) trial,[14] a multisite study conducted in the United Kingdom, compared add-on LTG to placebo in 202 BD-I and BD-II patients aged 16 years or older with acute depression, who were previously treated with QTP monotherapy. The study was a 2×2 factorial design in which patients were also simultaneously randomised to either folic acid or folic acid placebo. Improvement was assessed via the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16). Efficacy data were analysed based on modified ITT. Mean QIDS-SR16 scores after 12 weeks, the primary outcome, were lower for add-on LTG than for placebo, but the difference did not reach significance (mean diff. −1.73, 95% CI = −3.57 to 0.11, $p=0.066$). Post hoc analysis suggested that this may have been influenced by low or undetectable LTG serum levels in non-responders: a main effect of LTG at 12 weeks was apparent when these patients were excluded.[59] After 22 weeks, data for the 125 patients who remained in the study showed a similar difference in mean QIDS-SR16 scores between groups (mean diff. −1.87, 95% CI = −3.92 to 0.17, $p=0.072$). After 52 weeks, data for 103 patients showed significantly lower QIDS-SR16 scores for patients treated with LTG (mean diff. −2.69, 95% CI = −4.89 to −0.49, $p=0.017$). More patients taking LTG than taking placebo met criteria for remission (QIDS $\leqslant 5$) at Week 12 (31% *vs* 16%, $p=0.026$) and at Week 52 (36% *vs* 13%, $p=0.012$). Analysis of data from 150 patients randomised to receive folic acid or folic acid placebo showed an interaction between folic acid and LTG that was associated with impaired response during the first 12 weeks of treatment. The mean difference in QIDS-SR16 scores in patients not receiving folic acid was −4.14 (95% CI = −6.90 to −1.37, $p=0.004$) compared to a mean difference of 0.12 (95% CI = −2.58 to 2.82, $p=0.931$) in patients who did receive folic acid (see also later).

A 12-week, double-blind RCT compared adjunct LTG to placebo in 49 adults with rapid-cycling BD-I or BD-II who were experiencing a hypomanic, manic, mixed or depressed episode which was inadequately treated with Li + divalproex.[30] Patients were considered to be very ill, with high rates of co-occurring anxiety disorder (74%), past suicide attempts (40%) and previous psychotic diagnosis. Analysis of efficacy outcomes was based on LOCF. Adjunct LTG failed to separate from placebo on the primary outcome, change from baseline MADRS ($p=0.24$) or ANCOVA of change in baseline MADRS with baseline scores as a covariate ($p=0.34$). There were no differences between groups in response rate ($\geqslant$50% decrease in MADRS from baseline), bimodal response (MADRS $\leqslant 19$, YMRS $\leqslant 12$ and GAF $\geqslant 51$ maintained over four consecutive weeks), or remission (MADRS score $\leqslant 10$ at endpoint). After adjusting for treatment, time and age, a significant effect of diagnosis (BD-I *vs* BD-II) on YMRS scores was revealed with BD-I patients showing greater mean reductions compared to patients with BD-II ($p=0.01$). Serious AEs were reported in two patients (2%) receiving LTG: imminent suicidality in one patient and the emergence of a serious depressive episode requiring hospitalisation in the other.

Finally, a 12-week randomised, double-blind pilot study comparing adjunct LTG with adjunct citalopram in 20 patients with BD-I or BD-II who were previously treated with a first-line mood stabiliser,[35] found significant improvements in MADRS total score with both drugs (LTG −13.3, $p=0.001$; citalopram −14.2, $p=0.002$) and no significant difference between drugs ($p=0.78$).

Full efficacy data for placebo-controlled RCTs are available in the online supplementary material.

Systematic reviews and meta-analyses. Geddes *et al.*[60] aggregated data from the five industry-sponsored RCTs in acute depression including the single published study summarised above.

Analysis indicated a significantly greater number of responders with LTG than placebo for both HAM-D (relative risk (RR) = 1.27, $p = 0.002$) and MADRS (RR = 1.22, $p = 0.005$), and significant improvement in HAM-D and MADRS in patients with more severe baseline depression when analysed separately. The overall pooled treatment effect was modest, however. Significant improvements in HAM-D ($p = 0.001$) and MADRS ($p = 0.008$) in patients with baseline HAM-D > 24 almost certainly reflected the lower placebo response in this subgroup, rather than indicating greater efficacy *per se*. The high placebo response in moderately affected patients contributed to a result for this subgroup that did not reach statistical significance ($p = 0.445$), but numerical response rates were similar for LTG patients in each group. Analysis of patient-response data for all patients resulted in an NNT of 11. Excluding the moderately affected patients, the NNT for patients with more severe depression fell to 7.

A factor analytic study which analysed changes in sub-components of the 31-item HAM-D based on data from two RCTs, the first the industry-sponsored study summarised above, and the other in-patients with major depressive disorder,[61] was able to provide a more specific indication of the antidepressive profile of LTG.[62] Out of seven factors identified from the HAM-D ('depressive cognitions', 'psychomotor retardation', 'insomnia', 'hypersomnia', 'appetite and weight change', 'anxiety' and 'anergia'), it was determined that LTG displayed significant therapeutic effects with regard to 'depressive cognitions' (from Week 3) and 'psychomotor retardation' (from Week 4) in the patients with BD.

A separate broad analysis of data from placebo-controlled studies of LTG in bipolar and unipolar depression[63] showed greater improvement in depressive symptoms and greater treatment response for LTG than placebo. Efficacy did not differ significantly between bipolar and unipolar depression or between LTG monotherapy and adjunct LTG. In drug-to-drug comparisons, efficacy, response rates and remission rates did not differ significantly from Li, OFC, citalopram or inositol.

Meta-analytic comparisons of LTG with other treatments for bipolar depression have tended to favour other medications. A 2014 analysis[64] recommended against the use of LTG based on data from 29 double-blind RCTs including the published and unpublished manufacturer data and the study by van der Loos *et al.* summarised above. Medications were compared for treatment effect size and rate of 'switch-to-mania'. OLA and OFC recorded the largest effect sizes for efficacy. OFC was also associated with the highest response rate. Switch to mania was least likely with ziprasidone followed by QTP. LTG was found to have lower efficacy and the highest risk of switch-to-mania based on SUCRA (surface area under the cumulative ranking curve) ranking estimates. It should be noted that differences between drugs in switch to mania were not statistically significant, and there is no clear evidence that LTG precipitates a switch to a manic state.

A second meta-analysis published in the same year[65] which included the five industry-sponsored trials of LTG also recommended OFC as the most effective monotherapy for acute bipolar depression. The resulting hierarchy of treatments ranked OFC > QTP > carbamazepine (CBZ) > OLA > VPA > LTG > aripiprazole ≥ Li based on the average rates of improvement across placebo-controlled RCTs. LTG did not show statistically significant superiority over placebo according to drug-placebo standardised mean differences ($p = 0.09$). LTG was one of five medications with relatively unfavourable values for NNT (≥10).

Similarly, the results of a systematic review of RCTs of medication for BD-I depression ranked QTP highest with regard to efficacy, followed by OLA, OFC and divalproex. LTG did not show significantly greater improvement in MADRS/HAM-D total scores than placebo.[66]

Open-label studies. Two industry-sponsored open-label studies[51,52] reported significant improvement from baseline in patients entering the studies with either mania or depression. Calabrese *et al.*[51] reported significant improvements from baseline in HAM-D and MRS scores (both $p < 0.0001$) with significant improvements noted within 7 days for patients with current depressive or manic episodes. Bowden *et al.*[52] reported significant improvements from baseline in both depressive and manic symptoms among patients with and without rapid cycling. Rapid-cycling patients with index mania improved less than patients without rapid cycling, but improvements in patients with index depression were similar between rapid-cycling and non-rapid-cycling groups.

A 52-week open-label extension[53] to one of the pre-licencing RCTs in patients with acute BD-I depression[20] reported significant improvement in MADRS ($p < 0.05$) by Week 4 in LTG-treated patients who had received placebo in the acute study. Sustained improvements up to Week 52 were seen in new initiators and those maintained on LTG following the acute trial; 81.4% of patients were in remission within 4 weeks of starting LTG. Evidence of a reduction in mood instability also emerged: fewer than one-third of patients reported a manic event during the trial, compared with more than 60% who had reported a manic/hypomanic or mixed episode in the 12 months prior to starting LTG. Non-serious rash was the most common AE leading to withdrawal ($n = 6$; 5%).

More recently, a 52-week naturalistic study of add-on LTG in refractory patients with BD-II depression reported a sustained significant reduction in CGI-BP-S scores from Week 4 ($p = 0.001$), a response rate of 64.5% at Week 12, and improvements maintained for up to 1 year.[55] Discontinuation rates for all patients were 44.0% at Week 24 and 50.5% at Week 52 (14.3% and 22.9% in responders). Kaplan–Meier estimates for mean time to all-cause discontinuation were 31.8 weeks (95% CI 27.8–35.9) for all patients and 44.7 weeks (95% CI 41.1–48.3) for responders.

A Japanese observational study[56] reported findings for 445 patients with BD-I, BD-II or BD not otherwise specified (BD-NOS) who received LTG for 12 months (or until withdrawal), in most cases (77.5%), to supplement existing medication. Outcome measures were the Himorogi Self-Rating Depression Scale (HSDS), Himorogi Self-Rating Anxiety Scale and CGI-I. Improvements were reported by Week 4. HSDS scores were significantly reduced at Weeks 24 and 52 (both $p < 0.001$). When analysed separately, patients with BD-II and BD-NOS, but not patients with BD-I, showed significant improvement in HSDS. CGI-I ratings at endpoint (Week 52 or withdrawal) were 'very much improved' or 'much improved' in 62% of all patients. Although the median adherence rate was 399 days, 25% of patients had withdrawn within 28 days. It is not clear whether these withdrawals might have been due to skin rash, which tends to occur in the early weeks of treatment.

A study in 20 adolescents with BD-I, BD-II or BD-NOS and current depression[54] treated participants with LTG monotherapy or adjunct LTG for 8 weeks. At endpoint, 16 participants out of 19 with evaluable data (84%) met primary response criteria (a CGI-I score of 1 or 2), and 11 participants (58%) were considered to be in remission (CGI-I of 1 or 2 and CDRS-R score $\leqslant 28$). Significant decreases were reported in CDRS-*R* ($p = 0.001$), YMRS ($p = 0.001$) and Overt Aggression Scale – Modified Aggression ($p = 0.02$), Irritability ($p < 0.001$) and Suicidality ($p = 0.02$) scores. A significant reduction in CDRS-R was evident at the end of Week 1 ($p = 0.04$), although this was subsequently lost between Weeks 2 and 3. No significant weight change, rash or other AEs were reported.

A 12-week retrospective chart review[67] in 37 paediatric patients with unipolar depression ($n = 22$) or BD-I, BD-II (combined $n = 4$) or BD-NOS ($n = 11$) and current depression reported significant improvements in CGI-S scores ($p < 0.001$) and response (CGI-S $\leqslant 2$) in 17 patients (45.9%). Mild to moderate rash was reported in five patients (13.5%) and resolved in each case on withdrawal of LTG. Finally, a 'mirror-image' comparison of patient symptom profiles before and after initiation of LTG[57] found no significant change in the number of manic, depressive or mixed episodes, or the number of switches from depression to mania, and no significant improvements in CGI-BP, YMRS, Inventory of Depressive Symptomatology-Clinician or GAF scores. Although symptoms did not appear to improve, the mean duration of depressive and mixed episodes was significantly reduced ($p = 0.006$ and $p < 0.001$, respectively).

In addition to these studies, two open-label comparisons between LTG and other medications for depression have been published. Nierenberg *et al.*[49] found similar improvements with add-on LTG, risperidone or inositol in 66 refractory BD-I and BD-II patients with index depression. No significant differences in response rate at 16 weeks were found between any of the groups (LTG 23%, risperidone 6.4%, inositol 17.4%), despite a positive trend in favour of LTG. LTG was associated with lower depression ratings and lower CGI-S and GAF scores at endpoint than either inositol or risperidone. Nolen *et al.*[50] compared add-on LTG to tranylcypromine in 19 patients with refractory bipolar depression. The response rate without switch to mania was 62.5% for tranylcypromine and 36.4% for LTG, although the sample size was inadequate for a meaningful statistical comparison. Small sample

sizes in each of these studies may have limited the power of statistical analysis to separate the treatments.

Acute mania/hypomania. Table 4 shows a summary of study characteristics for the RCTs and open-label studies of LTG for acute mania/hypomania reviewed in this section.

Randomised, controlled trials. Two placebo-controlled RCTs of LTG monotherapy for bipolar mania were conducted in the pre-licencing period but neither published findings.

Data from three unpublished trials have been summarised in a review by Yatham.[70] The first compared LTG to placebo in a sample of 16 manic/hypomanic patients who had been treated unsuccessfully with Li. LTG was no more effective than placebo after 8 weeks. The other studies compared LTG to Li and placebo, the first as monotherapy and the second as add-on therapy in patients treated with antipsychotics. Neither study found LTG to be superior to placebo.

However, a short-term double-blind RCT comparing LTG and Li in 30 hospitalised patients with BD-I mania[36] found that both drugs improved acute manic symptoms within 4 weeks. Mania Rating Scale (MRS) scores decreased by 20.1 points for LTG ($p = 0.0002$) and 18.4 points for Li ($p = 0.0005$). The medications did not differ significantly either in efficacy or in the use of rescue medication (lorazepam) at any time point. Although a more rapid titration than is recommended for LTG was used in order to overcome some of the limitations of the short trial period there were no reports of rash in patients receiving LTG. However, the sample was small. Surprisingly, improvements in mania were similar to those seen with Li. However, Li serum levels were slightly below the therapeutic range during the observation period and the small sample may have limited the power of the analysis to detect differences between medications.

As also summarised above, a double-blind, placebo-controlled RCT in non-responsive rapid-cycling BD-I and BD-II patients with current hypomanic, manic, mixed or depressive episode[30] found adjunct LTG was no better than placebo for response, bimodal response (MADRS $\leqslant 19$, YMRS $\leqslant 12$ and GAF $\geqslant 51$ maintained over four consecutive weeks), remission or mean change in MADRS. Participants were considered seriously ill and had failed to respond to a combination of Li and divalproex. A subgroup analysis found BD-I patients had a significantly greater ($p = 0.01$) mean reduction in YMRS scores than BD-II patients.

Full efficacy data for placebo-controlled RCTs are available in the online supplementary material.

Meta-analyses. A 2011 meta-analysis evaluated the efficacy of 13 treatments for mania and placebo, on the basis of direct and indirect comparisons between drugs.[71] Five direct comparisons including LTG were identified, two placebo-controlled studies and three comparisons with Li. Standardised mean differences (95% CI) for continuous efficacy outcomes were estimated as 0.21 (−0.02 to 0.50) for LTG *vs* Li and 0.01 (−0.21 to 0.22) for LTG *vs* placebo, where positive values favour LTG. The estimated odds ratio (95% CI) for response rate for LTG *vs* Li was 0.76 (0.18 to 3.23), favouring Li. In the multiple treatments meta-analysis with placebo as the reference treatment, the mean change score standardised mean difference (95% credibility index) for LTG *vs* placebo was −0.08 (−0.34 to 0.18), where values <0 favour LTG. For response rate, an odds ratio (95% credibility index) of 0.73 (0.14–3.85) was calculated, where values <1 favour LTG. LTG was not significantly more effective than placebo on either efficacy measure.

A second meta-analysis of published and unpublished data from short-term randomised placebo-controlled trials and drug-to-drug comparisons in acute bipolar mania identified only a single placebo-controlled trial for LTG and concluded that the available evidence suggested LTG to be largely ineffective.[72]

Open-label studies. Two industry-sponsored open-label studies[51,52] reported significant improvement from baseline in patients entering the studies with either mania or depression. Calabrese *et al.*[51] reported significant improvements from baseline in HAM-D and MRS scores (both $p < 0.0001$) with significant improvements noted within 7 days for patients with current manic or depressive episodes. Bowden *et al.*[52] reported significant improvements from baseline in both manic and depressive symptoms in patients with and without rapid cycling. Rapid-cycling patients with index mania improved less than patients without rapid cycling.

A prospective open-label study of LTG monotherapy in 39 paediatric patients with acute bipolar

Table 4. Summary of acute mania studies.

Study	Type	Bipolar subtype	Monotherapy or adjunct	Comparator	N	Duration	LTG dose (mg/d)
Ichim *et al.*[36]	Double-blind, randomised, controlled trial	BD-I	Monotherapy	Li	30	4 weeks	100
Kemp *et al.*[30]	Randomised, double-blind, placebo-controlled study	Rapid-cycling BD-I; BD-II[a]	Adjunct (Li + DVX)	Placebo	49	12 weeks	150–200
Calabrese *et al.*[51]	Open-label, prospective, multi-centre trial	BD-I; BD-II; BD-NOS	Either	NA	75	48 weeks	50–500
Bowden *et al.*[52]	Open-label, multi-centre trial	BD-I; BD-II; Rapid-cycling	Either	NA	75	48 weeks	100–500
Born *et al.*[57]	Open-label, retrospective, and prospective study	BD-I; BD-II; Rapid-cycling	Either (Li; CBZ; VPA; TPM)	NA	20	⩽24 months	100–500
Biederman *et al.*[68]	Open-label, prospective study (paediatric patients)	BD-I; BD-II; BD-NOS	Monotherapy	NA	39	12 weeks	[b]
Kessing *et al.*[69]	Observational, register based, cohort study	BD-I, BD-II	Monotherapy	Li	730	—	—

BD, bipolar disorder; CBZ, carbamazepine; DVX, divalproex; LTG, lamotrigine; Li, lithium; NA, not applicable; NOS, not otherwise specified; TPM, topiramate; VPA, sodium valproate.
[a]Included patients with acute mania/hypomania, mixed episodes, or depression.
[b]Dose based on weight. Max 400 mg/day (children < 12 years); 300–500 mg/day (adolescents ⩾ 12 years).

mood elevation[68] found statistically significant improvements in mania (YMRS; $p=0.001$), depression (CDRS; $p=0.0002$), ADHD ($p=0.0001$) and psychosis ($p=0.0001$) over 12 weeks. Significant improvements in YMRS were reported as early as Week 1 with further significant improvements seen in subsequent weeks. At endpoint, 66% of patients had at least a 30% reduction in baseline YMRS and 54% at least a 50% reduction. Six patients discontinued treatment due to rash.

A 'mirror-image' comparison of patient symptom profiles before and after initiation of LTG[57] found no significant change in the number of manic, depressive or mixed episodes or significant improvements in CGI-BP, YMRS, Inventory of Depressive Symptomatology-Clinician or GAF scores.

Finally, a register-based cohort study[69] compared rates for 'switch-to' and 'add-on' of other psychotropics (antidepressants, antipsychotics and ASMs) and the rate of psychiatric hospitalisation in patients treated with either LTG or Li in clinical practice. LTG was associated with a higher overall rate of switch-to or add-on of other psychotropics than patients treated with Li (HR = 2.60; 95% CI 2.23–3.04) regardless of index mood episode. The overall rate of psychiatric hospitalisation was also higher for LTG-treated patients (HR = 1.45; 95% CI 1.28–1.65), with higher rates for both depressive index episodes (HR = 1.31; 95% CI 1.01–1.70) and manic index episodes (HR = 1.65; 95% CI 1.31–2.09).

AEs in placebo-controlled RCTs and open-label studies

Detailed information on the frequencies of treatment-emergent AEs was available for nine of the placebo-controlled RCTs, including a total of 668 patients. Table 5 shows the most frequently reported AEs with LTG in these nine studies, after adjustment for occurrence rates in patients treated with placebo. After adjustment, the most common AEs were nausea (3.6%), rash (2.7%), headache (2.3%) and insomnia (1.8%). A total of 76 AEs considered to be serious and/or leading to withdrawal were reported across the 13 placebo-controlled RCTs in a total of 873 patients randomised to LTG. The most frequent of these were rash ($n=15$) and emergence of a manic/

Table 5. Frequency of adverse events reported in placebo-controlled trials..

Adverse event	LTG *N* = 668 (*n*, %)	PLB *N* = 552 (*n*, %)	LTG–PLB (%)
Nausea	86 (12.9)	51 (9.2)	3.6
Rash	48 (7.2)	25 (4.5)	2.7
Headache	141 (21.1)	104 (18.8)	2.3
Insomnia	41 (6.1)	24 (4.3)	1.8
Accidental injury	17 (2.5)	6 (1.1)	1.5
Abdominal pain	11 (1.6)	4 (0.7)	0.9
Oropharyngeal pain	10 (1.5)	4 (0.7)	0.8
Pruritus	11 (1.6)	6 (1.1)	0.6
Suicidal ideation	4 (0.6)	0	0.6
Pulmonary problems	3 (0.4)	0	0.4
Hypertension	3 (0.4)	0	0.4

LTG, lamotrigine; PLB, placebo.

hypomanic or mixed episode ($n = 11$). Suicide-related events in patients treated with LTG were reported in six of the placebo-controlled RCTs,[20,25,26,28,30,31] three acute studies and three relapse/recurrence prevention studies. In the acute studies, there were three reports of suicidal ideation and eight suicide attempts. Excluding one study in which suicide-related events were systematically reported using the Columbia Suicide Severity Rating Scale (C-SSRS), there were 11 reports of suicidal ideation, two suicide attempts and four completed suicides in the relapse/recurrence prevention studies. The completed suicides were all reported in the same study, an 18-month monotherapy maintenance trial in recently depressed patients.[26] Two of the suicides occurred during the initial open-label phase, one during the randomised treatment phase in a patient receiving LTG 400 mg/day, and one 3 weeks after discontinuation from the open-label phase. None were considered related to study medication. In one adjunct LTG maintenance withdrawal trial in paediatric patients, suicide-related events were reported using the C-SSRS.[31] In this study, a total of 62 cases of suicidal ideation or suicidal behaviour were recorded in patients receiving LTG, 52 in the open-label phase and 10 in the randomised withdrawal phase. Five cases of serious suicidal ideation were reported during open-label treatment. Suicidal ideation led to withdrawal from the study of seven patients.

AEs reported in open-label trials were similar in type to those in the RCTs, with skin rash (11.1%), headache (4.7%), dizziness (4.0%), nausea (3.0%), somnolence (2.8%) and tremor (2.8%) the most common. Rash appeared in all cases within 6–8 weeks of treatment initiation and led to discontinuation in 26 patients from a total of 1776 patients treated with LTG (1.5%). Most of the open-label data on AEs came from a post-marketing surveillance study in Japan which monitored 989 patients for 52 weeks.[40] Skin rash was reported in 90 patients (9.1%) among whom there were eight cases which were considered serious, and two cases of Stevens–Johnson Syndrome (SJS). In total, there were 52 incidences of serious AEs in 33 patients, with rash the most common. Other serious AEs reported in at least two patients included pyrexia ($n = 4$), irritability, drug reaction with eosinophilia and systemic symptoms, renal impairment (all $n = 3$), abnormal hepatic function, stomatitis, erythema and erythema multiform (all $n = 2$). Suicide-related events and self injury were reported in five patients.

Discussion

Main findings

Based on the evidence from the placebo-controlled studies presented in this review, there appears to be moderately good evidence for the efficacy of LTG monotherapy for prolonging time to relapse/recurrence of any mood episode or of depressive episodes in patients with BD-I; of the five relapse/recurrence prevention studies, significant differences in primary outcome between LTG and placebo were reported in two monotherapy trials each with more than 50 patients in the LTG arm.[25,26] There is less evidence supporting adjunct LTG for relapse/recurrence, in particular in certain patient groups. Specifically, adjunct LTG was no better than placebo for prolonging time to additional pharmacotherapy in patients with rapid-cycling BD-I or BD-II or time to a bipolar event in paediatric patients younger than 13 years with BD-I. Evidence of efficacy for acute depression is equivocal, with only one study with a reasonably large sample ($\geqslant 100$), in which LTG was used as an adjunct to Li in patients with BD-I or BD-II, reporting significantly greater improvement in the primary outcome.[27] One

other study, this time in patients with BD-I or BD-II treated concomitantly with QTP, found adjunct LTG was effective in patients who were not also receiving folic acid but not in patients who were receiving folic acid.[14] Four other studies of adjunct LTG in patients treated with baseline paroxetine, fluoxetine and Li + divalproex did not find significantly greater improvement with adjunct LTG than with adjunct placebo.[22,24,28,30] However, all were small studies and tended to include patients with characteristics suggestive of more severe illness. In two studies, patients had rapid-cycling symptoms,[28,30] and in one of these, patients also had a recent substance use disorder.[28] Of two monotherapy trials for acute depression, only one found significantly greater improvement on the primary outcome[23]; in the other, the efficacy of LTG compared with placebo approached significance based on LOCF with a dose of 200 mg/day, but not 50 mg/day.[20] There is little published data on efficacy for acute mania, and no strong evidence from placebo-controlled trials. The single placebo-controlled trial that was identified was in patients with rapid-cycling with either acute mania/hypomania, mixed episode or depression who were non-responsive to treatment with Li + divalproex.[30] Based on change from baseline in YMRS scores, LTG was no better than placebo for mania in this study. Similarly, studies of adjunct LTG for acute depression[28,30] or maintenance treatment in patients with rapid-cycling symptoms failed to demonstrate efficacy.[21]

Comparison with current guidelines

Current treatment guidelines are broadly in agreement but are not always consistent with the evidence presented in the current review, or reflective of current licencing. The most recently updated are the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)[73] guidelines which were revised in 2018. LTG is included among first-line options for depression in both the acute and maintenance phases of BD-I, either as monotherapy or in combination with other drugs. In BD-II, LTG is considered a first-line option for maintenance treatment and a second-line option for acute depression. The 2016 British Association for Psychopharmacology (BAP) guidelines,[74] recommend LTG for the initial treatment of acute depressive episodes, either as monotherapy or in combination with medication to prevent manic relapse, and for the long-term treatment of bipolar depression and depressive relapse prevention in BD-I and BD-II. The 2014 guidelines of the UK National Institute for Health and Care Excellence (NICE) include LTG monotherapy among options for the management of moderate or severe bipolar depression in adults not currently treated with medication, and as an adjunct in unresponsive patients taking Li or sodium valproate (VPA).[75] Finally, the 2013 World Federation of Societies of Biological Psychiatry (WFSBP) guidelines assign a recommendation grade (RG) of 1 for long-term maintenance treatment[76] and an RG of 3 for acute BD-I depression,[77] where 1 is the most preferred option on a 5-point scale. The separate WFSBP guidelines for the treatment of acute and long-term mixed states, updated in 2017, do not recommend LTG.[78]

LTG is not commonly recommended for the treatment of mania due to the lack of demonstrated efficacy[79] and many guidelines, including the NICE guidance, specifically recommend against its use. The guidelines of the International College of Neuropsychopharmacology (CINP) suggest that add-on LTG may be beneficial in the early treatment of manic episodes in patients with predominant depressive polarity to prevent future depressive episodes, but in keeping with the broader consensus, LTG monotherapy is not recommended either for acute or maintenance treatment of mania.[80] By consensus, LTG monotherapy may be considered in BD-II but usually requires combination with an antimanic long-term agent in BD-I.

It is noteworthy that several of the current guidelines, including the NICE guidelines, recommend LTG for acute bipolar depression, either as monotherapy or adjunct to Li or VPA, despite mixed efficacy results in the clinical trials. LTG is not licenced for the acute treatment of depression in the United States, European Union or United Kingdom and the need for gradual dose titration in order to mitigate the risk of developing skin rash may limit its practicality for acute episodes[81] (see Table 6). A summary of the recommendations regarding LTG from current treatment guidelines for BD are available in the online supplementary material.

Although, according to meta-analytic comparisons, alternative medications might be preferred on the basis of efficacy alone, in particular for

Table 6. Comparison of review efficacy findings, NICE guidelines and licenced indications for bipolar disorder.

	Review findings	NICE guidelines	UK (EMC)	EU (EMA)	US (FDA)
Prevention of relapse/ recurrence	Moderate to good evidence for the prevention of depressive relapse/ recurrence	No recommendation. Li monotherapy recommended as first-line maintenance treatment	Prevention of depressive episodes in adult patients (⩾18 years) with bipolar I disorder with predominantly depressive episodes	Prevention of mood episodes in adult patients (⩾18 years) with bipolar disorder with predominantly depressive episodes	Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy
Acute depression	Low to moderate evidence	Monotherapy for moderate or severe bipolar depression in adult patients who have not responded to OFC or QTP monotherapy, or who prefer treatment with LTG. Adjunct therapy for moderate or severe bipolar depression in adult patients already taking Li or VPA who have not responded to adjunct OFC or adjunct QTP, or who prefer adjunct treatment with LTG	Not indicated	Not indicated	Effectiveness in acute treatment of mood episodes not established
Acute mania	No strong evidence	Negative recommendation	Not indicated	Not indicated	Treatment of acute mania or mixed episodes not recommended

EMA, European Medicines Agency; EMC, electronic medicines compendium; EU, European Union; FDA, Food and Drug Administration; Li, lithium; LTG, lamotrigine; NICE, National Institute for Health and Care Excellence; OFC, olanzapine/fluoxetine combination; QTP, quetiapine; VPA, sodium valproate.

acute bipolar phases, LTG may offer particular advantages among mood-stabilising drugs. LTG is a Class-B stabiliser which acts to stabilise mood from baseline sub-euthymic (depressed) states.[82,83] Compared with antidepressants, LTG appears to present a much lower risk of switch to mania, suggesting it may be a practical alternative, or supplementary, treatment for acute bipolar depression and prevention of depressive relapse, especially in cases characterised by frequent phase changes.[20,21,51,84] Many patients with BD are likely to require multiple drug regimes for adequate symptom control. LTG adjunct to Li[27] and QTP[14] has demonstrated efficacy for acute depression in placebo-controlled studies, but there is little evidence of efficacy for adjunct LTG in the maintenance phase of treatment.

AEs

The most frequent AEs in the placebo-controlled trials included in the current review were nausea, rash, headache and insomnia. LTG appeared to be well tolerated in these studies, with few reports of serious AEs. Earlier reviews[85,86] support these findings and suggest LTG is associated with comparatively infrequent and typically mild or moderate adverse reactions. A 2004 analysis of RCT data indicated a similar AE profile to placebo.[85] Specifically, no association with de-stabilised mood, sexual AEs, weight gain or withdrawal symptoms was found, and few serious AEs were reported. The incidence of serious skin rash was 0.1%. A more recent review of long-term data[87] found no difference in the incidence of AEs between doses of 50 mg/day and doses >200mg/day and LTG was well tolerated, even at the higher maintenance doses. Safety in paediatric patients has been reviewed by Egunsola *et al.*[88] In the audited studies, the majority having been in patients with epilepsy, rash was the most common AE (7.3%). Headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia were also reported. SJS

was rare, with an incidence of 0.09 per 1000 patients. Cutaneous adverse reactions with ASMs are likely to be more prevalent in children.[89] A review of RCTs of add-on LTG in epilepsy[90] reported serious rash (including SJS) in 0.8% of paediatric patients compared to 0.3% in adults.

US Food and Drug Administration (FDA) investigations have raised two specific concerns with regard to LTG safety, The first warning was issued in 2008 over the risk of suicidal ideation and/or suicidal behaviour with 11 ASMs, including LTG.[91]A manufacturer-conducted meta-analysis[92] found no significant increase in suicide-related events with LTG (1.2%) compared to placebo (0.9%), however, and the methodology behind the study that led to the warning has been challenged in subsequent independent analyses.[93] A separate study[32] has reported a higher rate of 'suicidal and self-injurious behaviour' with LTG than with OFC (LTG 3.4%; OFC 0.5%; $p = 0.037$).

In April 2018, the FDA issued a drug safety communication for the risk of hemophagocytic lymphohistiocytosis, a rare but potentially fatal systemic immune reaction,[94] as a result of eight identified cases associated with LTG, one of which resulted in fatality.

Patient acceptability appears to be favourable. ZarZar *et al.*[95] analysed quality of life and patient satisfaction data from a sample of 1139 BD-I patients participating in a 12-week open-label study. Quality-of-life scores improved significantly with LTG ($p < 0.0001$) and patient satisfaction with treatment increased from 34% at baseline to 58% at Week 12. Weight gain and sedation may be of particular concern to patients and are notably associated with treatment with OLA, OFC and QTP,[96–98] although patients receiving VPA[99] or Li[100] may also be affected. LTG is considered 'weight-neutral'[101] and has a substantially lower risk of weight gain than OLA, OFC or QTP.[102,103] A comparison of NNH/NNT ratios (likelihood to help or harm, LHH) for LTG and FDA-approved options for acute bipolar mania and depression[103] found lower levels of sedation (NNH = 42 *vs* 6–12) and weight gain (NNH = −34 *vs* 6–9) for LTG (negative values indicate a greater propensity to harm for placebo), but also lower efficacy (NNT = 12 *vs* 4–6). However, efficacy:sedation ratios ($LHH_{SEDATION}$) favoured LTG over QTP ($LHH_{SEDATION} = 3.5$ *vs* 1.0) and efficacy: weight gain ratios favoured LTG over OFC ($LHH_{WEIGHT} = -2.8$ *vs* 1.5). A study comparing weight gain data from RCTs of LTG and Li[104] found baseline obese patients gained more weight with Li while those taking LTG lost weight on average. There were no significant differences in weight gain between drugs in non-obese patients. LTG appears less deleterious to cognitive functioning than CBZ, VPA, topiramate or zonisamide[105,106] and may be associated with cognitive improvement in some patients.[107,108]

Rash. A particular concern with LTG is the incidence of skin rash; up to 10% of patients develop adverse skin reactions according to reviews.[109,110] Risk factors include high initial dose, rapid titration, co-medication with VPA, prior history of ASM-associated rash and age <13 years.[109,110] Analysis of data from 11 industry-sponsored RCTs and one long-term open-label study in bipolar and unipolar depression calculated a rate of benign rash in the controlled trials of 8.3% in LTG-treated patients and 6.3% in controls.[111] One case of serious rash was reported with LTG. In the open-label study, 13.1% of patients developed rash, including two serious cases. One 'mild' case of SJS was reported. A rash rate of 9% was calculated based on aggregated data from the two long-term placebo-controlled maintenance trials, compared to 8% in the combined placebo groups.[42] A more recent review of clinical trial data[90] reported serious rash in 0.08% of bipolar adults treated with LTG monotherapy and 0.13% treated with LTG as part of combination therapies. A more extensive analysis of RCTs of LTG monotherapy in BD, epilepsy or other conditions reported adverse skin reactions in 8.3% of a total sample of 18,968 patients. The rate of SJS/TEN was 0.04%, equivalent to one case for every 2,500 patients. The incidence of rash, including SJS/TEN, did not differ significantly between disorders, suggesting no genetic predisposition.[112] A review[113] of data from the manufacturer safety database from the launch of LTG in 1991 to 2015 identified 3454 cases of severe cutaneous adverse reactions (SCARS), of which 122 had a fatal outcome (considered attributable or non-attributable to LTG). At the time of the report, the estimated cumulative exposure to LTG was >8.4 million patient-years.

In two recent long-term open-label studies in BD, the rate of skin disorders was 13%−14% over 12 months in patients newly commenced on LTG.[40,56] In both studies, the current recommendations for initial dose and titration appear to have been followed in the majority of patients.

The first study[56] reported rash in 13.7% of patients. In the second study,[40] the rate of all skin disorders (including rash) was 13.1%, most frequently occurring during the first 8 weeks of treatment. A similar rate was found in a naturalistic study in Korea in 237 adult BD-I patients not previously treated with LTG.[114] Over 12 weeks, the incidence of rash was 12.7% and the incidence of serious rash was 0.8%. No cases of SJS or TEN were reported. Rash was not significantly associated with co-medication (including VPA), although patients who developed rash had significantly lower baseline weight (60.2 ± 10.1 kg) than those who did not (64.6 ± 11.3 kg) ($p = 0.048$). The majority (80%) of cases emerged within the first 6 weeks.

Restarting LTG after rash. The summary of product characteristics (SmPC) for LTG recommends discontinuation as soon as rash appears, regardless of severity, unless it is determined to be clearly unrelated to treatment.[115] The summary of product characteristics recommends against re-challenge except in cases where the potential benefit clearly outweighs the risk. Data on restarting LTG after discontinuation due to benign rash is sparse. A 2009 review identified 39 reported cases in which re-challenge with LTG was successful, all but two of which were in patients with epilepsy, and five cases of recurrence following reintroduction. A 2010 case series and meta-analysis involving a total of 48 re-challenge cases reported successful reintroduction without further rash in 85%.[116] The risk of recurrence of rash following re-challenge was increased when LTG was reintroduced within 4 weeks of the initial rash (36% *vs* 7%, $p = 0.002$). In the case series of 27 patients, all with BD, re-challenge was successful in 22 patients (82%). LTG was restarted at an initial dose of 5 mg/day (5 mg every other day in patients receiving VPA) and increased by 5 mg every two weeks up to 25 mg/day. Subsequently, LTG was increased in line with the manufacturer's recommended titration schedule. The delay between discontinuation and re-challenge in cases of successful reintroduction ranged from 1 week to ~520 weeks. A study in children with epilepsy[117] reported 100% success with reintroduction in seven patients with an initial dose of 0.1 mg/day and incremental dose escalation over the first 12 weeks (Table 7). Other case series have reported successful re-challenge with higher initial doses. Tavernor *et al.*[118] described eight cases in which LTG was restarted at doses between 0.5 mg on alternate days (one patient) and 25 mg/day with delays between withdrawal and re-challenge of between two and 35 months. Six of the patients had no recurrence of rash following reintroduction.

Table 7. Titration schedule for re-challenge with lamotrigine following rash (from Besag *et al.*[117]).

Week 1	0.1 mg daily
Week 2	0.1 mg bd
Week 3	0.2 mg bd
Week 4 and 5	1 mg daily
Week 6 and 7	2 mg daily
Week 8	4 mg daily
Week 9 and 10	6.25 mg daily
Week 11 and 12	12.5 mg daily
From Week 13	Double dose at intervals of no less than 2 weeks up to 50 mg
	No subsequent individual dose increase of greater than 50 mg
	Dose increase at intervals of no less than 2 weeks

In cases in which LTG is discontinued for shorter periods than might be required following rash, the manufacturers guidelines recommend that if the delay in restarting LTG exceeds 5 half-lives (mean half life for single-dose LTG in healthy subjects = 32.8 hrs (range 14.0–103.0 h). 5 × 32.8 = 164 h/6.8 days), the initial dosing recommendations and guidelines be followed, that is an initial dose of 25 mg/day for the first 2 weeks in patients not taking either VPA or CBZ.[115,119] In light of the increased risk of rash with high initial doses and/or rapid titration, the prescribing information for LTG states that the greater the delay in restarting LTG, the more consideration should be given to low dose and gradual escalation at reintroduction.[115,119]

Pregnancy and breast feeding

Mood stabilisers taken during pregnancy are associated with an increased risk of congenital malformations and perinatal complications (see Galbally *et al.*[120] for a review). The safety of LTG in pregnancy and the risk of congenital malformations and other neonatal AEs remains unclear,[121] although evidence suggests a lower risk than for other ASMs.[122–125] LTG carries a pregnancy safety rating of C in the United States, defined as

'animal studies show evidence of adverse foetal effects, but no adequate studies in humans–benefits of use in pregnancy may still outweigh risks'. A systematic review[126] estimated the overall risk of any major congenital malformation with LTG monotherapy at 2%−3%, although it is unclear whether this represents a greater risk than that for the general population.[127] A systematic review focusing on child developmental outcomes[128] found no evidence of particular risk to infant IQ or specific cognitive skills with prenatal exposure to LTG when compared to other ASMs or placebo. LTG also appears to be associated with a lower risk of impaired infant motor skills and socialisation than VPA.[129] There is evidence of a substantially greater risk of congenital malformation with LTG in combination with VPA than with LTG monotherapy.[126,130–134] A few reports have suggested elevated risk of oral clefts, hypospadias and gastrointestinal defects,[131,135,136] although the evidence is inconsistent.[123,131,133,137,138] A recent meta-analysis[139] found no significant differences in rates of miscarriage, stillbirth, preterm delivery or small-for-gestational-age (SGA) neonates between pregnancies with LTG exposure and pregnancies in the general population.

Although the majority of studies have shown no dose-related effect,[121] the guidelines of the International College of Neuropsychopharmacology indicate doses >200 mg/day[80] may increase the risk of teratogenic effects. Dose adjustments may be required during and following pregnancy to maintain efficacy.[140,141]

Much of the data on LTG exposure during pregnancy comes from epilepsy studies. It is not known whether epilepsy carries an inherently greater risk of congenital malformations, independent of ASM exposure; however, one study found five or more tonic-clonic seizures during pregnancy was associated with lower infant verbal IQ.[142] Moreover, evidence suggesting greater risk with ASMs than with no medication[121] may be subject to confounding factors; for example, unmedicated participants are likely to have milder epilepsy.

There are few reports of adverse consequences for neonatal health with indirect exposure to LTG. A review of LTG exposure in breast-feeding infants[141] found plasma concentrations ranging between 6% and 50% of maternal serum levels. Dose was not correlated with infant serum levels, albeit with wide variability between individuals. A single case of brief sleep apnoea associated with LTG exposure through breast milk has been reported.[143]

Interactions

Drug–drug interactions involving LTG as indicated by the BNF and of possible relevance to patients with BD are summarised in Table 8. Salient among these are interactions with VPA and CBZ.[144] Particular attention should be drawn to the interaction with VPA. VPA inhibits LTG metabolism, resulting in an up to three-fold increase in elimination half life[145,146] and the potential for substantial increase in LTG blood levels, typically two to four times,[147] which could lead to acute LTG toxicity. The clinical implication of this is that the LTG dose will usually need to be decreased to allow for the interaction. VPA should only be added to LTG after careful planning, taking into account existing recommendations. Conversely, enzyme-inducing medications such as CBZ may accelerate LTG metabolism[148] and decrease LTG levels which might necessitate an increase in LTG dose. There is also a theoretical interaction between LTG and antidepressant medications such as sertraline, which might increase LTG levels, but there appears to be limited clinical data on this. A review of drug-drug interactions of potential clinical relevance in BD concluded that interactions between LTG and SSRIs and LTG and antipsychotic medications are mild and not likely to be clinically relevant.[149] Therapeutic drug monitoring has, however, suggested evidence of an interaction with fluoxetine resulting in a significantly lower LTG concentration–dose ratio.[150] Lithium, the ASMs phenytoin, phenobarbital, topiramate and the contraceptive ethynilestradiol are also associated with lower LTG concentration–dose ratios.[147,150,151] LTG may affect serum levels of other drugs indicated for BD with some evidence of lower QTP concentration–dose ratios in patients co-administered LTG.[152,153] Reviews of drug–drug interactions involving newer ASMs found that LTG was involved in both the highest number of interactions with other ASMs ($n = 17$)[154] and the highest number of interactions with non-ASMs ($n = 22$).[155]

In addition to the drug–drug interactions already described, the package insert for LTG warns of possible teratogenic effects as a result of folate reductions due to prenatal exposure to LTG; however, the data come from *in vitro* and animal

Table 8. LTG interactions..

Drug	Risk	Severity of interaction	Manufacturer recommendation
Carbamazepine	Decreases LTG exposure. LTG may increase CBZ exposure	Moderate	Adjust LTG dose. Monitor CBZ
Combined hormonal contraceptives	Affects LTG exposure	Moderate	Adjust dose
Desogestrel	Increases LTG exposure	Moderate	No recommendation
Hormone replacement therapy	Predicted to affect LTG exposure	Moderate	No recommendation
Oxcarbazepine	Predicted to decrease LTG exposure. LTG predicted to increase OXC exposure	Moderate	Adjust dose. Monitor AEs
Valproate	Increases LTG exposure	Severe	Adjust dose. Monitor rash
Agomelatine, amisulpride, amitriptyline, aripiprazole, asenapine, benperidol, cariprazine, chlorpromazine, clomipramine, clozapine, dosulepin, doxepin, droperidol, esketamine, flupentixol, fluphenazine, haloperidol, imipramine, levomepromazine, lofepramine, loxapine, lurasidone, mianserin, mirtazapine, nortriptyline, olanzapine, paliperidone, pericyazine, pimozide, promazine, quetiapine, risperidone, sulpiride, trazodone, trimipramine, venlafaxine	LTG and listed drugs can cause CNS depressant effects	NA	NA

AEs, adverse events; CBZ, carbamazepine; CNS, central nervous system; LTG, lamotrigine; NA, not applicable; OXC, oxcarbazepine.

studies and significant changes in circulating folate with LTG not been observed in humans. Of note, the development of LTG as an ASM was predicated on the hypothesis that folate might be pro-convulsive, although this was never substantiated, and that LTG might indeed act as a folate antagonist.[156] Evidence of inhibition of LTG by folic acid, emerged as an unexpected finding in the CEQUEL study[14] and may be of potential clinical relevance if substantiated by further studies. A post hoc analysis[59] discounted a pharmacokinetic effect (LTG levels were unaffected by folic acid) but suggested a possible genetic association, with affected patients found to be carriers of the catechol-O-methyltransferase (COMT) Met polymorphism related to one-carbon metabolism. These findings remain to be confirmed, however, and the authors advised caution over their interpretation.

Balance of benefits and risks

Consideration of risk–benefit ratios may favour LTG over other medications. An analysis of 22 placebo-controlled RCTs in patients with acute bipolar depression[157] compared ASMs, antidepressants, antipsychotics and Li for efficacy and tolerability. Pooled results for ASMs (LTG, CBZ and VPA) indicated greater efficacy (NNT = 5.06) than for antidepressants (NNT = 5.75), antipsychotics (NNT = 8.25) or Li (NNT = 15.00) but differences in NNT between medication groups were not statistically significant. LTG was better tolerated (NNH = 23.6) than either CBZ (NNH = 8.80) or VPA (NNH = 4.92) and had a superior benefit/risk ratio (NNH/NNT: LTG = 4.10; CBZ = 2.56; VPA = 1.12). Modern antidepressants were less effective (NNT = 7.43) than ASMs but had better tolerability (NNH = 1080) and the most favourable risk/

benefit ratio (NNH/NNT = 145). Antipsychotics demonstrated reasonable efficacy (pooled NNT = 8.25) but had low tolerability (pooled NNH = 4.89). Li was less effective (NNT = 15.0) but well tolerated (NNH = 38.0), based on data from a single RCT.[157]

Dose in the 13 placebo-controlled studies ranged between 50 and 500 mg/day (most commonly 200 mg/day), and there was little clear evidence of a dose–response relationship above 200 mg/day. Studies have found improvement in adults with doses of 200–500mg/day.[21,25,158,159] In one of the industry-sponsored trials which compared doses of 50 and 200 mg/day, the lower dose failed to produce a notable therapeutic effect.[20] A case study[160] investigating the effect of increasing dose from 200 to 300 mg/day found significant improvements in Beck Depression Inventory and GAF scores with the higher dose. Studies in paediatric patients have found LTG to be effective at approximate mean doses of 131–200 mg/day.[38,54] The BNF recommends an initial dose for adults of 25 mg/day for the first 2 weeks, increased to 50 mg/day for a further 2 weeks with subsequent increases of up to 100 mg every 1–2 weeks until the required dose is reached. Maintenance doses are typically 100–200 mg/day in one or two divided doses and may be increased to up to 400 mg/day.[161] Titration schedule and dose considerations may be affected by co-medication; in particular, more gradual escalation and lower maintenance doses are recommended in patients taking VPA, and higher starting and maintenance doses in patients taking enzyme-inducing medications without VPA.[161]

There is a potential risk of suicide during the titration period of any drug used to treat depressive illness before therapeutic doses are reached. Due to its longer titration period than for other antidepressant medication, this risk may be elevated with LTG. We were unable to find any cases in the placebo-controlled trials which might provide clear evidence of a particular risk with LTG, however.

The reference range for LTG in mood disorders is considered to be between 5 and 11 μg/mL (5–11 mg/L),[162] but there is little data specifically for BD.[163] An open-label study of LTG add-on therapy in refractory bipolar patients treated concurrently with VPA[164] reported improvement within a few days, and plasma levels after total remission of 1.9–6.2 mg/L. In a more recent study, LTG serum levels at baseline and at time of remission were compared in 12 patients with BD-II depression.[165] After excluding one patient taking VPA, no linear relationship was apparent between serum LTG and improvement, suggesting serum level did not strongly influence effectiveness. A retrospective analysis of therapeutic drug monitoring data[166] noted that the therapeutic reference range (TRR) observed in BD is often that recommended for epilepsy (3000–14,000 ng/mL (3–14 mg/L)). However, analysis of data from the KONBEST therapeutic drug monitoring database found that of 360 patients prescribed LTG for BD, 82 demonstrated improvement, but only 32 of these had LTG serum concentrations within the TRR for epilepsy. The remaining 50 patients had lower serum levels, the lowest recorded as 177 ng/mL. The mean (SD) serum level in the 82 patients who improved was 3341 (2563) ng/mL (i.e. towards the lower end of the TRR for epilepsy). No positive linear correlation between serum level and CGI-I score could be statistically validated. Comparing CGI-I scores of 2 or 3 ('much improved' or 'minimally improved') to LTG levels showed that a higher concentration apparently led to a better therapeutic response, although again the difference could not be statistically validated. The authors concluded that lower serum levels than for epilepsy appear to have a therapeutic effect in BD. LTG doses ranged between 25 and 400 mg/day.[166] Since these studies were either retrospective analyses or open-label trials, the results may be subject to confounding by undocumented placebo effects.[76]

Limitations

Limitations of current evidence. The efficacy of LTG in BD has been systematically studied, but when considered separately by bipolar phase and by monotherapy or adjunct therapy trials, there were few placebo-controlled studies for any particular indication or treatment regime. A degree of divergence between studies with regard to patient samples (e.g. bipolar diagnosis, comorbidities, severity of illness and prior exposure to medication for mood disorders) and study characteristics (e.g. sample size and duration) was also apparent. The majority of placebo-controlled studies were of adjunct LTG which reflects the multi-drug treatments most likely to be employed in clinical practice. Not all combinations involving LTG have shown efficacy in placebo-controlled trials, but there were too few studies for each combination in comparable samples to conclude whether

some combinations may be more effective than others in the general population of patients with BD. Adjunct studies tended to include patients with baseline characteristics suggesting more severe illness, including rapid-cycling, which might limit the generalisability of the findings.

Available evidence comes largely from patients with BD-I. Few studies have focused on BD-II, in part reflecting the greater difficulty in reaching a reliable BD-II diagnosis.[167] Only one placebo-controlled study was identified in which the sample was composed entirely of patients with BD-II, a trial of adjunct LTG in 23 patients with acute depression. Small samples in this and several of the other controlled studies may have lacked adequate statistical power. In open studies in BD-II, LTG has demonstrated efficacy for the treatment of acute depression.[167] However, the sparsity of Class-I evidence specific to BD-II has resulted in consensus-based treatment guidelines regarding LTG that follow those established for BD-I, or that omit BD-II. The lack of clarity regarding efficacy in BD-II is also reflected in the regulatory approval for LTG, which applies only to BD-I. There was a similar lack of studies in paediatric patients for which only a single placebo-controlled study was identified. Paediatric BD exhibits distinct characteristics[168] which suggest treatment strategies deployed in adults may not be equally effective in children.

Of note, the studies which informed licencing of LTG for maintenance treatment featured enriched samples, meaning that only patients who demonstrated tolerability and mood stability with open-label LTG were subsequently randomised. This may limit the generalisability of the findings from these studies. Moreover, some authors have questioned whether maintenance studies assessed genuine prophylaxis, as opposed to relapse prevention, due to the relatively short period of stabilised mood prior to randomisation.[169]

Just over half of the 13 placebo-controlled RCTs were judged to be poor quality according to the Cochrane risk of bias AHRQ standards. Only three studies were considered to be good quality. A third of studies had unclear risk of selection bias due to inadequate reporting of random sequence generation and/or allocation concealment. Over half were considered to have unclear or high risk of attrition bias due to incomplete outcome data. Seven of the 13 studies stated that efficacy data were analysed on the basis of ITT or modified ITT. However, it was not clear whether all of these studies met the accepted criteria for ITT analysis.[170]

In addition to these considerations, there is scant data available from independently conducted trials; eight of the 13 RCTs mentioned in this review were supported by industry grants and two further RCTs included authors with a current (at the time of publication) or past affiliation with the manufacturer. Moreover, there is a risk of publication bias with regard to the industry-sponsored RCTs, many of which were unpublished.

Limitations of the current review. The aim of the current review was to be a comprehensive examination of the current evidence for efficacy. However, only studies which were available as full-text versions in English were considered for inclusion. This may have resulted in the omission of relevant data. Similarly, the search was limited to published data; several of the pre-licencing studies have not been published and data from these studies were not considered, except where included as part of the summary of earlier meta-analyses. No separate meta-analysis was performed as part of this review; most of the included RCTs have been included in previous analyses (summary available in the supplementary material).

Conclusion

LTG is an established treatment for BD with a range of therapeutic advantages over some alternative options for mood stabilisation and maintenance treatment. Opinion varies, however, with regard to the relative efficacy of LTG compared to other drugs. The strongest evidence exists for LTG monotherapy for the prevention of recurrence and relapse, particularly depressive relapse, in stabilised patients. Some evidence suggests efficacy in acute bipolar depression, in particular in combination with Li or QTP. There is no strong evidence to support use in acute mania, and the need for an extended titration period to reduce the risk of rash may, in practical terms, also limit clinical utility in acute depressive episodes, in particular in monotherapy regimes. There is scant evidence from RCTs to support use in BD-II and paediatric populations, although the available data, largely from open-label studies have sometimes been promising. Placebo-controlled trials in patients with rapid-cycling symptoms have not found evidence of efficacy in either acute or maintenance phases. LTG may be most effective in combination with other mood stabilisers, antidepressants or

antipsychotics; however, the placebo-controlled trial evidence in support of LTG for maintenance treatment comes solely from two monotherapy studies. In clinical practice, most patients with BD are likely to be treated with multiple drug regimes. Safety, tolerability, and patient acceptability are all relatively favourable, although the risk of serious rash should be recognised and mitigated by compliance with recommendations for dosing and titration. In particular, when LTG is added to valproate, the dose-escalation rate should follow the slower rate recommended. There is limited information on safety in pregnancy in bipolar patients, but the extensive evidence from patients treated for epilepsy indicates one of the lowest foetal malformation rates among ASMs. On the balance of efficacy and tolerability, LTG might be considered a first-line drug for BD, except for acute manic episodes or where rapid symptom control is required. In terms of efficacy alone, LTG has demonstrated benefit as maintenance treatment; however, for acute depressive episodes the evidence favours other medications.

Author contributions

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References

1. Goodwin FK and Jamison KR. *Manic-depressive illness: bipolar disorders and recurrent depression*. Oxford: Oxford University Press, 2007.
2. World Health Organization. *International statistical classification of diseases and related health problems (10th revision)*. 2nd ed. 2010, https://icd.who.int/browse10/
3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders fourth edition (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association, 2000.
4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders fifth edition (DSM-5)*. 5th ed. Washington, DC: American Psychiatric Association, 2013.
5. Phillips M. Dysthymia and cyclothymia in ICD-11. *World Psychiatry* 2012; 11: 53–58.
6. Reed GM, First MB, Kogan CS, *et al*. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry* 2019; 18: 3–19. DOI: 10.1002/wps.20611.
7. Merikangas KR, Akiskal HS, Angst J, *et al*. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry* 2007; 64: 543–552. DOI: 10.1001/archpsyc.64.5.543.
8. Merikangas KR, Jin R, He J-P, *et al*. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; 68: 241–251. DOI: 10.1001/archgenpsychiatry.2011.12.
9. Bauer M and Pfennig A. Epidemiology of bipolar disorders. *Epilepsia* 2005; 46(Suppl. 4): 8–13. DOI: 10.1111/j.1528-1167.2005.463003.x.
10. López-Muñoz F, Shen WW, D'Ocon P, *et al*. A history of the pharmacological treatment of bipolar disorder. *Int J Mol Sci* 2018; 19: 2143. DOI: 10.3390/ijms19072143.
11. Weisler RH, Calabrese JR, Bowden CL, *et al*. Discovery and development of lamotrigine for bipolar disorder: a story of serendipity, clinical observations, risk taking, and persistence. *J Affect Disord* 2008; 108: 1–9. DOI: 10.1016/j.jad.2007.09.012.
12. Smith D, Baker G, Davies G, *et al*. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993; 34: 312–322. DOI: 10.1111/j.1528-1157.1993.tb02417.x.
13. GlaxoSmithKline. Annual report 2003. https//www.gsk.com/media/2669/annual-report-2003.pdf (accessed 12 September 2021).
14. Geddes JR, Gardiner A, Rendell J, *et al*. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 × 2 factorial randomised trial. *Lancet Psychiat* 2016; 3: 31–39. DOI: 10.1016/S2215-0366(15)00450-2.

15. Stahl SM, Morrissette DA, Faedda G, *et al.* Guidelines for the recognition and management of mixed depression. *CNS Spectr* 2017; 22: 203–219. DOI: 10.1017/S1092852917000165.

16. Harrison PJ, Cipriani A, Harmer CJ, *et al.* Innovative approaches to bipolar disorder and its treatment. *Ann N Y Acad Sci* 2016; 1366: 76–89. DOI: 10.1111/nyas.13048.

17. Ketter TA, Manji HK and Post RM. Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. *J Clin Psychopharmacol* 2003; 23: 484–495.

18. Hahn C-G, Gyulai L, Baldassano CF, *et al.* The current understanding of lamotrigine as a mood stabilizer. *J Clin Psychiatry* 2004; 65: 791–804.

19. Ng F, Hallam K, Lucas N, *et al.* The role of lamotrigine in the management of bipolar disorder. *Neuropsychiatr Dis Treat* 2007; 3: 463–474.

20. Calabrese JR, Bowden CL, Sachs GS, *et al.* A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999; 60: 79–88.

21. Calabrese JR, Suppes T, Bowden CL, *et al.* A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry* 2000; 61: 841–850. DOI: 10.4088/jcp.v61n1106.

22. Normann C, Hummel B, Scharer LO, *et al.* Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J Clin Psychiatry* 2002; 63: 337–344. DOI: 10.4088/jcp.v63n0411.

23. Obrocea GV, Dunn RM, Frye MA, *et al.* Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiat* 2002; 51: 253–260. DOI: 10.1016/S0006-3223(01)01206-9.

24. Barbosa L, Berk M and Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J Clin Psychiatry* 2003; 64: 403–407.

25. Bowden CL, Calabrese JR, Sachs G, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; 60: 392–400. DOI: 10.1001/archpsyc.60.4.392.

26. Calabrese JR, Bowden CL, Sachs G, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64: 1013–1024. DOI: 10.4088/jcp.v64n0906.

27. van der Loos ML, Mulder PG, Hartong EG, *et al.* Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 223–231.

28. Wang Z, Gao K, Kemp DE, *et al.* Lamotrigine adjunctive therapy to lithium and divalproex in depressed patients with rapid cycling bipolar disorder and a recent substance use disorder: a 12-week, double-blind, placebo-controlled pilot study. *Psychopharmacol Bull* 2010; 43: 5–21.

29. van der Loos ML, Mulder P, Hartong EG, *et al.* Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design. *Bipolar Disord* 2011; 13: 111–117. DOI: 10.1111/j.1399-5618.2011.00887.x.

30. Kemp DE, Gao K, Fein EB, *et al.* Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. *Bipolar Disord* 2012; 14: 780–789. DOI: 10.1111/bdi.12013.

31. Findling RL, Chang K, Robb A, *et al.* Adjunctive maintenance lamotrigine for pediatric bipolar I disorder: a placebo-controlled, randomized withdrawal study. *J Am Acad Child Adolesc Psychiatry* 2015; 54: 1020–1031. DOI: 10.1016/j.jaac.2015.09.017.

32. Brown EB, McElroy SL, Keck PE Jr, *et al.* A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 2006; 67: 1025–1033.

33. Brown E, Dunner DL, McElroy SL, *et al.* Olanzapine/fluoxetine combination vs. Lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol* 2009; 12: 773–782. DOI: 10.1017/S1461145708009735.

34. Suppes T, Marangell LB, Bernstein IH, *et al.* A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. *J Affect Disord* 2008; 111: 334–343. DOI: 10.1016/j.jad.2008.02.004.

35. Schaffer A, Zuker P and Levitt A. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar

depression. *J Affect Disord* 2006; 96: 95–99. DOI: 10.1016/j.jad.2006.05.023.

36. Ichim L, Berk M and Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; 12: 5–10. DOI: 10.3109/10401230009147081.

37. Licht RW, Nielsen JN, Gram LF, *et al.* Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). *Bipolar Disord* 2010; 12: 483–493. DOI: 10.1111/j.1399-5618.2010.00836.x.

38. Pavuluri MN, Henry DB, Moss M, *et al.* Effectiveness of lamotrigine in maintaining symptom control in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol* 2009; 19: 75–82. DOI: 10.1089/cap.2008.0107.

39. Pan PY, Lee MS, Lo MC, *et al.* Olanzapine is superior to lamotrigine in the prevention of bipolar depression: a naturalistic observational study. *BMC Psychiatry* 2014; 14: 145. DOI: 10.1186/1471-244x-14-145.

40. Terao T, Ishida A, Kimura T, *et al.* Assessment of safety and efficacy of lamotrigine over the course of 1-year observation in Japanese patients with bipolar disorder: post-marketing surveillance study report. *Neuropsychiatr Dis Treat* 2017; 13: 1441–1448.

41. Goldberg JF, Calabrese JR, Saville BR, *et al.* Mood stabilization and destabilization during acute and continuation phase treatment for bipolar I disorder with lamotrigine or placebo. *J Clin Psychiatry* 2009; 70: 1273–1280. DOI: 10.4088/JCP.08m04381.

42. Goodwin GM, Bowden CL, Calabrese JR, *et al.* A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* 2004; 65: 432–441.

43. Calabrese JR, Goldberg JF, Ketter TA, *et al.* Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. *Biol Psychiat* 2006; 59: 1061–1064. DOI: 10.1016/j.biopsych.2006.02.034.

44. Vieta E, Günther O, Locklear J, *et al.* Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol* 2011; 14: 1029–1049. DOI: 10.1017/s1461145711000885.

45. Oya K, Sakuma K, Esumi S, *et al.* 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. *Neuropsychopharmacol Rep* 2019; 39: 241–246. DOI: 10.1002/npr2.12056.

46. Popovic D, Reinares M, Goikolea JM, *et al.* Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. *Eur Neuropsychopharmacol* 2012; 22: 339–346. DOI: 10.1016/j.euroneuro.2011.09.008.

47. Swartz HA and Thase ME. Pharmacotherapy for the treatment of acute bipolar ii depression: current evidence. *J Clin Psychiatry* 2011; 72: 356–366. DOI: 10.4088/JCP.09r05192gre.

48. Frye MA, Ketter TA, Kimbrell TA, *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; 20: 607–614.

49. Nierenberg AA, Ostacher MJ, Calabrese JR, *et al.* Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiaty* 2006; 163: 210–216. DOI: 10.1176/appi.ajp.163.2.210.

50. Nolen WA, Kupka RW, Hellemann G, *et al.* Tranylcypromine vs. Lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. *Acta Psychiatr Scand* 2007; 115: 360–365. DOI: 10.1111/j.1600-0447.2007.00993.x.

51. Calabrese JR, Bowden CL, McElroy SL, *et al.* Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. *Am J Psychiaty* 1999; 156: 1019–1023. DOI: 10.1176/ajp.156.7.1019.

52. Bowden CL, Calabrese JR, McElroy SL, *et al.* The efficacy of lamotrigine in rapid cycling and non–rapid cycling patients with bipolar disorder. *Biol Psychiatry* 1999; 45: 953–958. DOI: 10.1016/S0006-3223(99)00013-X.

53. McElroy SL, Zarate CA, Cookson J, *et al.* A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression. *J Clin Psychiatry* 2004; 65: 204–210. DOI: 10.4088/JCP.v65n0210.

54. Chang K, Saxena K and Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry*

2006; 45: 298–304. DOI: 10.1097/01.chi.0000194566.86160.a3.

55. Chang JS, Moon E, Cha B, *et al.* Adjunctive lamotrigine therapy for patients with bipolar II depression partially responsive to mood stabilizers. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; 34: 1322–1326. DOI: 10.1016/j.pnpbp.2010.07.020.

56. Watanabe Y and Hongo S. Long-term efficacy and safety of lamotrigine for all types of bipolar disorder. *Neuropsychiatr Dis Treat* 2017; 13: 843–854.

57. Born C, Bernhard B, Dittmann S, *et al.* Lamotrigine in bipolar disorder: results of a mirror-image evaluation using the NIMH Lifechart-Methodology. *J Affect Disord* 2009; 115: 241–245. DOI: 10.1016/j.jad.2008.07.020.

58. Calabrese JR, Huffman RF, White RL, *et al.* Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 2008; 10: 323–333. DOI: 10.1111/j.1399-5618.2007.00500.x.

59. Tunbridge EM, Attenburrow MJ, Gardiner A, *et al.* Biochemical and genetic predictors and correlates of response to lamotrigine and folic acid in bipolar depression: analysis of the CEQUEL clinical trial. *Bipolar Disord* 2017; 19: 477–486. DOI: 10.1111/bdi.12531.

60. Geddes JR, Calabrese JR and Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009; 194: 4–9.

61. Laurenza A, Asnis G and Beaman M. A double-blind placebo-controlled study supporting the efficacy of lamotrigine in unipolar depression. *Bipolar Disord* 1999; 1: 39–40.

62. Mitchell PB, Hadzi-Pavlovic D, Evoniuk G, *et al.* A factor analytic study in bipolar depression, and response to lamotrigine. *CNS Spectr* 2013; 18: 214–224. DOI: 10.1017/s1092852913000291.

63. Solmi M, Veronese N, Zaninotto L, *et al.* 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 Spectr* 2016; 21: 403–418. DOI: 10.1017/s1092852916000523.

64. Taylor DM, Cornelius V, Smith L, *et al.* Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand* 2014; 130: 452–469. DOI: 10.1111/acps.12343.

65. Selle V, Schalkwijk S, Vazquez GH, *et al.* Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry* 2014; 47: 43–52. DOI: 10.1055/s-0033-1363258.

66. Vieta E, Locklear J, Gunther O, *et al.* Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol* 2010; 30: 579–590. DOI: 10.1097/JCP.0b013e3181f15849.

67. Shon SH, Joo Y, Lee JS, *et al.* Lamotrigine treatment of adolescents with unipolar and bipolar depression: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2014; 24: 285–287. DOI: 10.1089/cap.2013.0121.

68. Biederman J, Joshi G, Mick E, *et al.* A prospective open-label trial of lamotrigine monotherapy in children and adolescents with bipolar disorder. *CNS Neurosci Ther* 2010; 16: 91–102. DOI: 10.1111/j.1755-5949.2009.00121.x.

69. Kessing LV, Hellmund G and Andersen PK. An observational nationwide register based cohort study on lamotrigine versus lithium in bipolar disorder. *J Psychopharmacol* 2012; 26: 644–652. DOI: 10.1177/0269881111414091.

70. Yatham LN. Newer anticonvulsants in the treatment of bipolar disorder. *J Clin Psychiatry* 2004; 65: 28–35.

71. Cipriani A, Barbui C, Salanti G, *et al.* Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet* 2011; 378: 1306–1315. DOI: 10.1016/S0140-6736(11)60873-8.

72. Yildiz A, Vieta E, Leucht S, *et al.* Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology* 2011; 36: 375–389. DOI: 10.1038/npp.2010.192.

73. Yatham LN, Kennedy SH, Parikh SV, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; 20: 97–170. DOI: 10.1111/bdi.12609.

74. Goodwin G, Haddad P, Ferrier I, *et al.* Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology.

J Psychopharmacol 2016; 30: 495–553. DOI: 10.1177/0269881116636545.

75. National Collaborating Centre for Mental Health and National Institute for Health and Care Excellence: Clinical Guidelines. *Bipolar disorder: the NICE guideline on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care*. London: The British Psychological Society and The Royal College of Psychiatrists, 2014.
76. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry* 2013; 14: 154–219. DOI: 10.3109/15622975.2013.770551.
77. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 2010; 11: 81–109. DOI: 10.3109/15622970903555881.
78. Grunze H, Vieta E, Goodwin GM, *et al*. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry* 2018; 19: 2–58. DOI: 10.1080/15622975.2017.1384850.
79. Trankner A, Sander C and Schonknecht P. A critical review of the recent literature and selected therapy guidelines since 2006 on the use of lamotrigine in bipolar disorder. *Neuropsychiatr Dis Treat* 2013; 9: 101–111. DOI: 10.2147/NDT.S37126.
80. Fountoulakis KN, Grunze H, Vieta E, *et al*. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. *Int J Neuropsychopharmacol* 2017; 20: 180–195. DOI: 10.1093/ijnp/pyw109.
81. Sachs GS, Printz DJ, Kahn DA, *et al*. The expert consensus guideline series: medication treatment of bipolar disorder. *Postgrad Med* 2000; 1: 1–104.
82. Ketter TA and Calabrese JR. Stabilization of mood from below versus above baseline in bipolar disorder: a new nomenclature. *J Clin Psychiatry* 2002; 63: 146–151. DOI: 10.4088/jcp.v63n0210.
83. Herman E. Lamotrigine: a depression mood stabiliser. *Eur Neuropsychopharmacol* 2004; 14: S89–S93. DOI: 10.1016/j.euroneuro.2004.03.003.
84. Calabrese JR, Shelton MD, Bowden CL, *et al*. Bipolar rapid cycling: focus on depression as its hallmark. *J Clin Psychiatry* 2001; 62: 34–41.
85. Bowden CL, Asnis GM, Ginsberg LD, *et al*. Safety and tolerability of lamotrigine for bipolar disorder. *Drug Saf* 2004; 27: 173–184. DOI: 10.2165/00002018-200427030-00002.
86. Miura T, Noma H, Furukawa TA, *et al*. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* 2014; 1: 351–359. DOI: 10.1016/S2215-0366(14)70314-1.
87. Sogawa R, Mochinaga S, Inaba T, *et al*. Safety of long-term use of lamotrigine for the treatment of psychiatric disorders. *Clin Neuropharmacol* 2016; 39: 295–298. DOI: 10.1097/wnf.0000000000000174.
88. Egunsola O, Choonara I and Sammons HM. Safety of lamotrigine in paediatrics: a systematic review. *BMJ Open* 2015; 5: e007711. DOI: 10.1136/bmjopen-2015-007711.
89. Fabrazzo M and Tortorella A. Safety and tolerability of mood stabilizers. In: Spina E and Trifirò G (eds) *Pharmacovigilance in psychiatry*. Cham: Springer International Publishing, 2016, pp. 209–232.
90. Seo HJ, Chiesa A, Lee SJ, *et al*. Safety and tolerability of lamotrigine: results from 12 placebo-controlled clinical trials and clinical implications. *Clin Neuropharmacol* 2011; 34: 39–47. DOI: 10.1097/WNF.0b013e3182055c07.
91. Gibbons RD, Hur K, Brown CH, *et al*. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Arch Gen Psychiatry* 2009; 66: 1354–1360. DOI: 10.1001/archgenpsychiatry.2009.159.
92. GlaxoSmithKline. *Lamotrigine suicidality pooled analysis: analysis of data in lamotrigine clinical trials for suicidality* (Review). Brentford: GlaxoSmithKline, 2007.
93. Hesdorffer DC and Kanner AM. The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? *Epilepsia* 2009; 50: 978–986. DOI: 10.1111/j.1528-1167.2009.02012.x.
94. US Food & Drug Administration. FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal), https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-immune-system-reaction-seizure-and-mental-health (accessed 6 January 2020).

95. ZarZar MN, Graham J, Roberts J, *et al.* Effectiveness and weight effects of open-label lamotrigine with and without concomitant psychotropic medications in patients with bipolar I disorder. *Medscape Gen Med* 2007; 9: 41–41.

96. Correll CU, Detraux J, De Lepeleire J, *et al.* Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry* 2015; 14: 119–136. DOI: 10.1002/wps.20204.

97. McIntyre RS, Cha DS, Kim RD, *et al.* A review of FDA-approved treatment options in bipolar depression. *CNS Spectr* 2013; (18, Suppl. 1): 4–20; quiz 21. DOI: 10.1017/S1092852913000746.

98. Cipriani A, Rendell JM and Geddes J. Olanzapine in long-term treatment for bipolar disorder. *Cochrane Database Syst Rev* 2009; 1: CD004367. DOI: 10.1002/14651858.CD004367.pub2.

99. Grootens KP, Meijer A, Hartong EG, *et al.* Weight changes associated with antiepileptic mood stabilizers in the treatment of bipolar disorder. *Eur J Clin Pharmacol* 2018; 74: 1485–1489. DOI: 10.1007/s00228-018-2517-2.

100. Ng F, Mammen OK, Wilting I, *et al.* The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disord* 2009; 11: 559–595. DOI: 10.1111/j.1399-5618.2009.00737.x.

101. Sachs G, Bowden C, Calabrese JR, *et al.* Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder. *Bipolar Disord* 2006; 8: 175–181. DOI: 10.1111/j.1399-5618.2006.00308.x.

102. Ketter TA, Miller S, Dell'Osso B, *et al.* Balancing benefits and harms of treatments for acute bipolar depression. *J Affect Disord* 2014; 169: S24–S33. DOI: 10.1016/S0165-0327(14)70006-0.

103. Srivastava S and Ketter TA. Clinical relevance of treatments for acute bipolar disorder: balancing therapeutic and adverse effects. *Clin Ther* 2011; 33: B40–B48. DOI: 10.1016/j.clinthera.2011.11.020.

104. Bowden CL, Calabrese JR, Ketter TA, *et al.* Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar i disorder. *Am J Psychiatry* 2006; 163: 1199–1201. DOI: 10.1176/ajp.2006.163.7.1199.

105. Daban C, Martínez-Arán A, Torrent C, *et al.* Cognitive functioning in bipolar patients receiving lamotrigine: preliminary results. *J Clin Psychopharmacol* 2006; 26: 178–181. DOI: 10.1097/01.jcp.0000204332.64390.f3.

106. Dias VV, Balanza-Martinez V, Soeiro-de-Souza MG, *et al.* Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. *Acta Psychiatr Scand* 2012; 126: 315–331. DOI: 10.1111/j.1600-0447.2012.01910.x.

107. Khan A, Ginsberg LD, Asnis GM, *et al.* Effect of lamotrigine on cognitive complaints in patients with bipolar I disorder. *J Clin Psychiatry* 2004; 65: 1483–1490.

108. Pavuluri MN, Passarotti AM, Mohammed T, *et al.* Enhanced working and verbal memory after lamotrigine treatment in pediatric bipolar disorder. *Bipolar Disord* 2010; 12: 213–220. DOI: 10.1111/j.1399-5618.2010.00792.x.

109. Guberman AH, Besag FMC, Brodie MJ, *et al.* Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia* 1999; 40: 985–991. DOI: 10.1111/j.1528-1157.1999.tb00807.x.

110. Wang X-q, Xiong J, Xu W-H, *et al.* Risk of a lamotrigine-related skin rash: current meta-analysis and postmarketing cohort analysis. *Seizure* 2015; 25: 52–61. DOI: 10.1016/j.seizure.2014.12.001.

111. Calabrese JR, Sullivan JR, Bowden CL, *et al.* Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 2002; 63: 1012–1019.

112. Bloom R and 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. *An Bras Dermatol* 2017; 92: 139–141. DOI: 10.1590/abd1806-4841.20175070.

113. Brickel N, Shaikh H, Kirkham A, *et al.* Collaboration in pharmacovigilance: lamotrigine and fatal severe cutaneous adverse reactions: a review of spontaneous reports. *Ther Clin Risk Manag* 2017; 13: 897–903. DOI: 10.2147/TCRM.S131021.

114. Woo YS, Bahk W-M, Jon D-I, *et al.* Rash in adult patients receiving lamotrigine to treat bipolar I disorder in Korea: a multicenter, prospective, naturalistic, open-label trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; 33: 1147–1152. DOI: 10.1016/j.pnpbp.2009.06.010.

115. The Electronic Medicines Compendium (EMC). Lamictal SmPC, https://www.medicines.org.

uk/emc/medicine/4228#INTERACTIONS (accessed 6 January 2020).

116. Aiken CB and Orr C. Rechallenge with lamotrigine after a rash: a prospective case series and review of the literature. *Psychiatry (Edgmont)* 2010; 7: 27–32.

117. Besag FMC, Ng GYT and Pool F. Successful re-introduction of lamotrigine after initial rash. *Seizure* 2000; 9: 282–286. DOI: 10.1053/seiz.2000.0394.

118. Tavernor SJ, Wong ICK, Newton R, *et al*. Rechallenge with lamotrigine after initial rash. *Seizure* 1995; 4: 67–71. DOI: 10.1016/S1059-1311(05)80082-2.

119. GlaxoSmithKline. Lamictal prescribing information. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF (accessed 12 September 2021).

120. Galbally M, Roberts M and Buist A. Mood stabilizers in pregnancy: a systematic review. *Aust N Z J Psychiatry* 2010; 44: 967–977. DOI: 10.3109/00048674.2010.506637.

121. Epstein RA, Moore KM and Bobo WV. Treatment of bipolar disorders during pregnancy: maternal and fetal safety and challenges. *Drug Healthc Patient Saf* 2015; 7: 7–29. DOI: 10.2147/DHPS.S50556.

122. Tomson T, Battino D, Bonizzoni E, *et al*. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *The Lancet Neurology* 2011; 10: 609–617. DOI: 10.1016/S1474-4422(11)70107-7.

123. Meador K, Reynolds MW, Crean S, *et al*. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008; 81: 1–13. DOI: 10.1016/j.eplepsyres.2008.04.022.

124. Morrell MJ, Hayes FJ, Sluss PM, *et al*. Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann Neurol* 2008; 64: 200–211. DOI: 10.1002/ana.21411.

125. Joffe H, Cohen LS, Suppes T, *et al*. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. *Biol Psychiatry* 2006; 59: 1078–1086. DOI: 10.1016/j.biopsych.2005.10.017.

126. Tomson T and Battino D. Teratogenic effects of antiepileptic drugs. *Lancet Neurol* 2012; 11: 803–813. DOI: 10.1016/S1474-4422(12)70103-5.

127. Cunnington M and Tennis P. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; 64: 955–960. DOI: 10.1212/01.Wnl.0000154515.94346.89.

128. Haskey C and Galbally M. Mood stabilizers in pregnancy and child developmental outcomes: a systematic review. *Aust N Z J Psychiatry* 2017; 51: 1087–1097. DOI: 10.1177/0004867417726175.

129. Deshmukh U, Adams J, Macklin EA, *et al*. Behavioral outcomes in children exposed prenatally to lamotrigine, valproate, or carbamazepine. *Neurotoxicol Teratol* 2016; 54: 5–14. DOI: 10.1016/j.ntt.2016.01.001.

130. Wyszynski DF, Nambisan M, Surve T, *et al*. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; 64: 961–965. DOI: 10.1212/01.Wnl.0000154516.43630.C5.

131. Morrow J, Russell A, Guthrie E, *et al*. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77: 193–198. DOI: 10.1136/jnnp.2005.074203.

132. Wide K, Winbladh B and Källén B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. *Acta Paediatr* 2004; 93: 174–176. DOI: 10.1111/j.1651-2227.2004.tb00701.x.

133. Vajda FJ, O'Brien TJ, Hitchcock A, *et al*. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. *J Clin Neurosci* 2003; 10: 543–549. DOI: 10.1016/S0967-5868(03)00158-9.

134. Kaaja E, Kaaja R and Hiilesmaa V. Major malformations in offspring of women with epilepsy. *Neurology* 2003; 60: 575–579. DOI: 10.1212/01.Wnl.0000044157.28073.Dc.

135. Holmes LB, Baldwin EJ, Smith CR, *et al*. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008; 70: 2152–2158. DOI: 10.1212/01.wnl.0000304343.45104.d6.

136. Dolk H, Jentink J, Loane M, *et al*. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology* 2008; 71: 714–722. DOI: 10.1212/01.wnl.0000316194.98475.d8.

137. Diav-Citrin O, Shechtman S, Zvi N, *et al*. Is it safe to use lamotrigine during pregnancy? A prospective comparative observational study.

Birth Defects Res 2017; 109: 1196–1203. DOI: 10.1002/bdr2.1058.

138. Sabers A, Dam M, A-Rogvi-Hansen B, *et al*. Epilepsy and pregnancy: lamotrigine as main drug used. *Acta Neurol Scand* 2004; 109: 9–13. DOI: 10.1034/j.1600-0404.2003.00200.x.

139. Pariente G, Leibson T, Shulman T, *et al*. Pregnancy outcomes following in utero exposure to lamotrigine: a systematic review and meta-analysis. *CNS Drugs* 2017; 31: 439–450. DOI: 10.1007/s40263-017-0433-0.

140. Polepally AR, Pennell PB, Brundage RC, *et al*. Model-based lamotrigine clearance changes during pregnancy: clinical implication. *Ann Clin Transl Neurol* 2014; 1: 99–106. DOI: 10.1002/acn3.29.

141. Clark CT, Klein AM, Perel JM, *et al*. Lamotrigine dosing for pregnant patients with bipolar disorder. *Am J Psychiatry* 2013; 170: 1240–1247. DOI: 10.1176/appi.ajp.2013.13010006.

142. Adab N, Kini U, Vinten J, *et al*. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2004; 75: 1575–1583. DOI: 10.1136/jnnp.2003.029132.

143. Nordmo E, Aronsen L, Wasland K, *et al*. Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother* 2009; 43: 1893–1897. DOI: 10.1345/aph.1M254.

144. Biton V. Pharmacokinetics, toxicology and safety of lamotrigine in epilepsy. *Expert Opin Drug Metab Toxicol* 2006; 2: 1009–1018. DOI: 10.1517/17425255.2.6.1009.

145. Kanner AM and Frey M. Adding valproate to lamotrigine: a study of their pharmacokinetic interaction. *Neurology* 2000; 55: 588–591. DOI: 10.1212/wnl.55.4.588.

146. Mataringa M-I, May TW and Rambeck B. Does lamotrigine influence valproate concentrations? *Ther Drug Monit* 2002; 24: 631–636.

147. Böttiger Y, Svensson J-O and Ståhle L. Lamotrigine drug interactions in a TDM material. *Ther Drug Monit* 1999; 21: 171–174.

148. Spina E, Pisani F and Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine. *Clin Pharmacokinet* 1996; 31: 198–214. DOI: 10.2165/00003088-199631030-00004.

149. de Leon J and Spina E. Possible pharmacodynamic and pharmacokinetic drug-drug interactions that are likely to be clinically relevant and/or frequent in bipolar disorder. *Current Psychiatry Reports* 2018; 20: 17. DOI: 10.1007/s11920-018-0881-3.

150. Reimers A, Skogvoll E, Sund JK, *et al*. Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. *J Clin Psychopharmacol* 2005; 25: 342–348. DOI: 10.1097/01.jcp.0000169418.31275.a7.

151. Grundmann M, Koristkova B, Brozmanova H, *et al*. Lamotrigine drug interactions in combination therapy and the influence of therapeutic drug monitoring on clinical outcomes of adult patients. *Ther Drug Monit* 2017; 39: 543–549. DOI: 10.1097/FTD.0000000000000433.

152. Andersson ML, Björkhem-Bergman L and Lindh JD. Possible drug–drug interaction between quetiapine and lamotrigine: evidence from a Swedish TDM database. *Br J Clin Pharmacol* 2011; 72: 153–156. DOI: 10.1111/j.1365-2125.2011.03941.x.

153. Castberg I, Skogvoll E and Spigset O. Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. *J Clin Psychiatry* 2007; 68: 1540–1545. DOI: 10.4088/jcp.v68n1011.

154. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)–part 1: pharmacokinetic and pharmacodynamic interactions between AEDs. *Clin Pharmacokinet* 2013; 52: 927–966. DOI: 10.1007/s40262-013-0087-0.

155. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)—part 2: pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. *Clin Pharmacokinet* 2013; 52: 1045–1061. DOI: 10.1007/s40262-013-0088-z.

156. Brodie MJ. Lamotrigine. *Lancet* 1992; 339: 1397–1400.

157. Vazquez GH, Holtzman JN, Tondo L, *et al*. Efficacy and tolerability of treatments for bipolar depression. *J Affect Disord* 2015; 183: 258–262. DOI: 10.1016/j.jad.2015.05.016.

158. Goldberg JF, Bowden CL, Calabrese JR, *et al*. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. *Biological Psychiatry* 2008; 63: 125–130. DOI: 10.1016/j.biopsych.2006.12.031.

159. Tsarkov A and Petlovanyi P. The role of lamotrigine in the treatment of bipolar depression. *Imp J Interdiscip Res* 2017; 3: 131–134.

160. Abraham PF. A case series of lamotrigine increased to 300mg daily in patients with

bipolar depression. *Asian J Psychiatr* 2011; 4: 223. DOI: 10.1016/j.ajp.2011.05.007.

161. British National Formulary. Lamotrigine, https://www.nice.org.uk/bnf-uk-only#indicationsAndDoses (accessed 6 January 2020).

162. Katayama Y, Terao T, Kamei K, *et al*. Therapeutic window of lamotrigine for mood disorders: a naturalistic retrospective study. *Pharmacopsychiatry* 2014; 47: 111–114. DOI: 10.1055/s-0034-1375618.

163. Lembke A. Optimal dosing of lithium, valproic acid, and lamotrigine in the treatment of mood disorders. *Primary Psychiatry* 2009; 16: 37.

164. Walden J, Hesslinger B, van Calker D, *et al*. Addition of lamotrigine to valproate may enhance efficacy in the treatment of bipolar affective disorder. *Pharmacopsychiatry* 1996; 29: 193–195.

165. Kikkawa A, Kitamura Y, Aiba T, *et al*. Correlation between the efficacy of lamotrigine and the serum lamotrigine level during the remission phase of acute bipolar II depression: a naturalistic and unblinded prospective pilot study. *Biol Pharm Bull* 2017; 40: 413–418. DOI: 10.1248/bpb.b16-00725.

166. Unholzer S and Haen E. Retrospective analysis of therapeutic drug monitoring data for treatment of bipolar disorder with lamotrigine. *Pharmacopsychiatry* 2015; 48: 211–214. DOI: 10.1055/s-0035-1559635.

167. Wong MMC. Management of bipolar II disorder. *Indian J Psychol Med* 2011; 33: 18–28. DOI: 10.4103/0253-7176.85391.

168. Biederman J, Mick E, Faraone SV, *et al*. Current concepts in the validity, diagnosis and treatment of paediatric bipolar disorder. *Int J Neuropsychopharmacol* 2003; 6: 293–300. DOI: 10.1017/s1461145703003547.

169. Fountoulakis KN, Yatham L, Grunze H, *et al*. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 2: review, grading of the evidence, and a precise algorithm. *Int J Neuropsychopharmacol* 2016; 20: 121–179. DOI: 10.1093/ijnp/pyw100.

170. McCoy CE. Understanding the intention-to-treat principle in randomized controlled trials. *West J Emerg Med* 2017; 18: 1075–1078. DOI: 10.5811/westjem.2017.8.35985.

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