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ORIGINAL RESEARCH

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

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Objectives. To meta-analytically summarize lamotrigine's effectiveness and safety in unipolar and bipolar depression.

Methods. We conducted systematic PubMed and SCOPUS reviews (last search =10/01/2015) of randomized controlled trials comparing lamotrigine to placebo or other agents with antidepressant activity in unipolar or bipolar depression. We performed a random-effects meta-analysis of depression ratings, response, remission, and adverse effects calculating standardized mean difference (SMD) and risk ratio (RR) ±95% confidence intervals (CIs).

Results. Eighteen studies (n = 2152, duration = 9.83 weeks) in patients with unipolar depression (studies = 4, n = 187; monotherapy vs lithium = 1, augmentation of antidepressants vs placebo = 3) or bipolar depression (studies = 14, n = 1965; monotherapy vs placebo = 5, monotherapy vs lithium or olanzapine + fluoxetine = 2, augmentation of antidepressants vs placebo = 1, augmentation of mood stabilizers vs placebo = 3, augmentation of mood stabilizers vs trancylpromine, citalopram, or inositol = 3) were meta-analyzed. Lamotrigine's efficacy for depressive symptoms did not differ significantly in monotherapy vs augmentation studies (vs. placebo: p = 0.98, I^2 = 0%; vs active agents: p = 0.48, I^2 = 0%) or in unipolar vs bipolar patients (vs placebo: p = 0.60, I^2 = 0%), allowing pooling of each placebo-controlled and active-controlled trials. Lamotrigine outperformed placebo regarding depressive symptoms (studies = 11, n = 713 vs n = 696; SMD = -0.15, 95% CI = -0.27, -0.02, p = 0.02, heterogeneity: p = 0.24) and response (after removing one extreme outlier; RR = 1.42, 95% CI = 1.13–1.78; p = 0.003, heterogeneity: p = 0.08). Conversely, lamotrigine did not differ regarding efficacy on depressive symptoms, response, or remission from lithium, olanzapine + fluoxetine, citalopram, or inositol (studies = 6, n = 306 vs n = 318, p-values = 0.85–0.92). Adverse effects and all-cause/specific-cause discontinuation were similar across all comparisons.

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Conclusions. Lamotrigine was superior to placebo in improving unipolar and bipolar depressive symptoms, without causing more frequent adverse effects/discontinuations. Lamotrigine did not differ from lithium, olanzapine + fluoxetine, citalopram, or inositol.

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Key words: Bipolar depression, bipolar disorder, lamotrigine, major depressive disorder, trials, unipolar depression.

Introduction

Unipolar depression and bipolar disorder, of which the main illness polarity is depression,[1–3] are among the most debilitating disorders worldwide.[4–6] While antidepressants are the mainstay of the pharmacologic management of unipolar depression,[7,8] the treatment of bipolar depression is much more contentious.[9,10] Since antidepressants may increase the risk of switch to mania,[11–13] bipolar depression is often treated with conventional mood stabilizers, such as lithium, antiepileptics, or second-generation antipsychotics,[14,15] either alone or in combination. However, depressive symptoms often respond insufficiently in bipolar disorder,[16] and even in unipolar depression.[17] Moreover, differentiating bipolar depression from unipolar depression can be a major clinical challenge, resulting in common misdiagnoses,[18–20] and consequently in inadequate treatment. Lamotrigine could be a valid option for both conditions. In fact, if the unipolar or bipolar nature of depressive symptoms cannot be determined, the use of antidepressant monotherapy, especially tricyclic antidepressants, is not recommended, according to the *primum non nocere* principle and guidelines.[10]

Lamotrigine is one of the agents that has been studied and used in both bipolar and unipolar depression due to its lack of mania induction,[21] but there is contrasting evidence about its efficacy and safety[22,23] in both bipolar depression and in unipolar depression.[24–26]

Several meta-analyses have investigated the role of lamotrigine in bipolar disorder and unipolar depression,[27–29] but to the authors' knowledge, none of these prior meta-analyses assessed the utility of lamotrigine when combining studies in both unipolar and bipolar depression. Considering both unipolar and bipolar disorder together can help to either determine significant differences in the effect sizes achieved with lamotrigine or, alternatively, in the absence of significant differences, can allow for the pooling of the data, thus providing more power for subgroup and meta-regression analyses.

The aim of this meta-analysis was therefore to investigate the efficacy and safety of lamotrigine in patients with unipolar and bipolar depression, either in monotherapy or used in combination with other psychotropic medications, compared to placebo or to other medications with antidepressant activity. Our hypothesis was that the efficacy of lamotrigine would not be significantly different in unipolar or bipolar depression, and that it would a well-tolerated and efficacious therapeutic option for both unipolar and bipolar depression.

Methods

This systematic review adhered to the PRISMA statement,[30] following a predetermined, but unpublished, protocol.

Search strategy

An electronic literature search was conducted in PubMed and SCOPUS from database inception until October 1, 2015, by 2 independent reviewers (M.S. and N.V.), using the search terms "(lamotrigine) AND (random* OR placebo) AND (depression OR depressed OR depressive OR bipolar)" to identify randomized controlled trials investigating the efficacy and safety of lamotrigine in patients diagnosed with unipolar or bipolar depression.

Inclusion and exclusion criteria

Included were randomized, controlled studies that (i) compared lamotrigine with placebo or another medication with antidepressant activity, (ii) included patients diagnosed with bipolar depression or unipolar depression, (iii) reported antidepressant efficacy data using a standardized rating scale, such as the Montgomery–Åsberg Depression Rating Scale (MADRS)[31] or Hamilton Depression Scale (HAMD)[32,33] 17, 21, or 31 items, and/or side effect data. Studies were excluded if they (i) were not randomized, (ii) did not have a control group, (iii) included patients who were not depressed, or (iv) did not report meta-analyzable data.

Outcomes

The primary outcome was depressive symptom change. Secondary outcomes included response, remission, all-cause and specific-cause discontinuation, and adverse events.

Data extraction

Two authors (M.S. and N.V.) independently extracted data from the included studies into a standardized

Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information was extracted: author; year; country; study design; inclusion and exclusion criteria; trial duration; sample size of efficacy and safety analyses; comorbidity; previous treatments; age at first depressive episode or number of previous depressive episodes; duration of current depressive episode; administered type and dose of medication(s); population demographics; baseline, follow-up, and change in depression rating scales; definition and rates of study completion; response; remission; side effects; study sponsor; funding source; and quality indicators. Whenever data were not reported or we needed clarification, we contacted the authors at least twice requesting additional information.

Quality assessment

Evaluation of methodological study quality was conducted by 2 independent authors (M.S. and N.V.) using the Cochrane Collaboration tool for assessing risk of bias.[34] The tool includes 6 domains that can indicate low, unclear, or high risk of bias. Considering the 6 domains, a study is defined as having low risk of bias when all domains indicate low risk of bias, unclear risk of bias when 1 or more domains indicates unclear risk of bias, and high risk of bias when high risk of bias is present for 1 or more key domains.

Data analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.1 for Windows (http://tech.cochrane.org/revman). All outcomes were meta-analyzed when at least 2 studies provided data for a given outcome. When combining studies, the random effects model[35] was used to account for study heterogeneity. For continuous data, we calculated standardized mean difference (SMD) with its 95% confidence interval (CI) as the effect size; for dichotomous data, we used risk ratio (RR) with its 95% CI. Study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p < 0.05$ and I-squared $\geq 50\%$ indicating significant heterogeneity.[36]

We compared baseline-to-endpoint depression rating scale value change (preferring last-observation-carried-forward change values), study-defined response and remission rates, and side-effect rates in studies comparing lamotrigine vs placebo and lamotrigine vs other agents with antidepressant activity.

In the lamotrigine vs placebo studies, 3 subgroup analyses were conducted (lamotrigine monotherapy, lamotrigine augmentation of mood stabilizers, and lamotrigine augmentation of antidepressants). In the studies of lamotrigine vs other agents with antidepressant activity, subgroup analyses were conducted according to lamotrigine monotherapy vs lamotrigine augmentation therapy of mood stabilizers (2 subgroups) and according to active comparator (up to 5 subgroups). In addition, in the lamotrigine vs placebo analyses, results were also compared in the unipolar vs bipolar depression subgroups. Since the most used depression rating scale was MADRS, MADRS values were used preferentially in the analysis when more than 1 depression rating scale was used in order to decrease heterogeneity. Since too few head-to-head studies existed for the comparison of lamotrigine vs other agents with antidepressant activity, subgroup analyses comparing results in studies of unipolar vs bipolar depression could not be conducted.

In the case that the change in depression symptoms (primary outcome) did not differ significantly and that the results were not significantly heterogeneous (ie, χ^2 $p < 0.05$ and $I^2 < 50\%$) in the 2 main subgroup analyses, ie, (i) by comparator (ie, lamotrigine as monotherapy vs augmentation of mood stabilizers vs augmentation of antidepressants) and (ii) by depression subgroup (ie, unipolar depression vs bipolar depression), we considered the pooled results across all placebo-controlled studies and separately all active-controlled studies as valid, allowing us to subsequently conduct a series of pre-planned, exploratory subgroup analyses using RevMan and mixed effects meta-regression analyses using Comprehensive Meta-Analysis V3 (http://www.meta-analysis.com). The subgroup analyses included double blind vs other studies, and also industry sponsorship: yes vs no. Meta-regression analyses investigated the following potential moderator variables: age, sex, white race, total baseline MADRS and total baseline HAMD scores, study duration, sample size, lamotrigine target dose, and mean endpoint lamotrigine dose.

Finally, for depressive symptom reduction and treatment response, funnel plots were visually inspected to assess for publication bias, Egger's test[37] and Begg–Mazumdar Kendall's tau[38] were used to determine if a publication bias was likely, and a leave-one-out sensitivity analysis was used in case of severe outliers to adjust the results for such possible outliers.

Results

Search results

The search strategy yielded 333 articles. After exclusion of 315 references at the title and abstract level, 18 papers were full-text reviewed. Altogether, 4 articles were excluded, either due to referring to the same sample (studies = 3[39–44]) or because of reporting on patients with mixed mania (study = 1[45]). One article[44] reported on pooled data from 5 trials (GW602/SCAB2001, GW603/SCAA2010,

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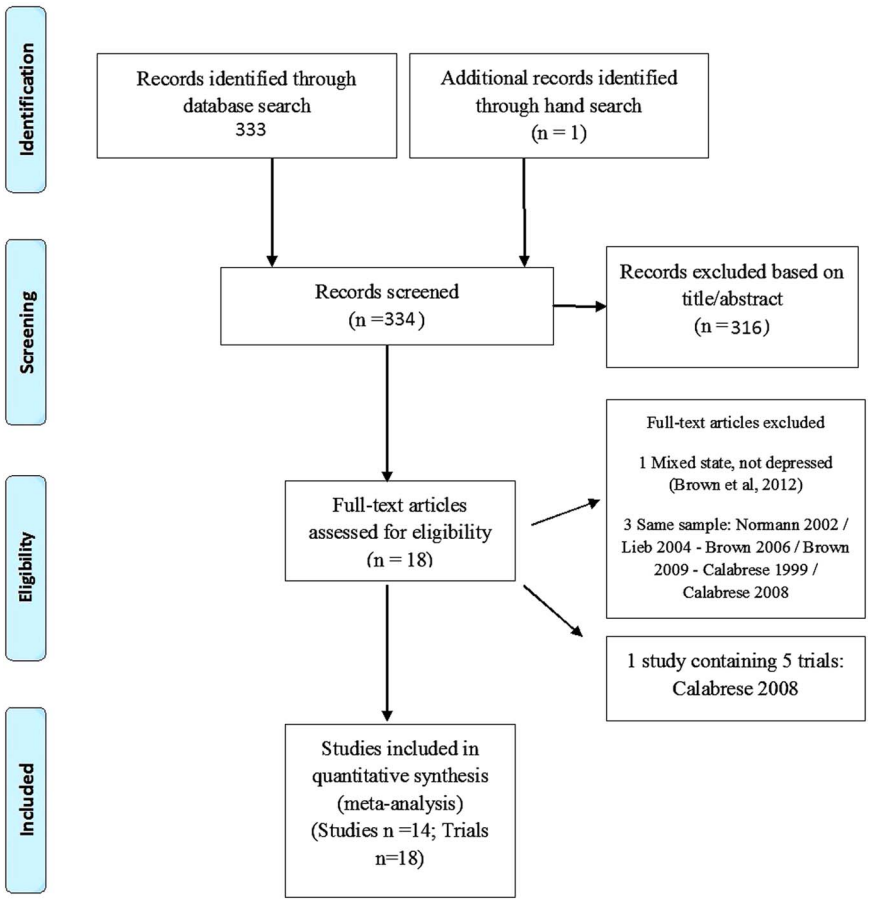

FIGURE 1. PRISMA Flow Diagram of Study Selection Process.

SCA100223, SCA30924, SCA40910), resulting in 14 articles reporting on 18 trials that were meta-analyzed (Figure 1).

Included studies, treatments, and participants

The detailed features of the included studies are described in Table 1. In the 18 trials (n = 2152), 1109 patients were randomized to lamotrigine and 1043 were randomized to placebo or an active comparator. All studies were randomized, 14 studies were double blind (n = 1970), 2 single blind[46,47](n = 124), and 2 were open label[48,49] (n = 67). The mean duration of the trials was 9.83 ± 2.77 weeks. The mean age of the sample was 39.47 ± 11.92 years old for lamotrigine-treated patients and 38.19 ± 12.52 years old for the respective control groups. In the lamotrigine group, participants were 56.5% female and 82.84% were white, and in the control groups, 56.41% were female and 83.31% were white.

Studies included 1948 patients with bipolar depression in 14 studies (bipolar I disorder only: studies = 4, n = 1121; bipolar II disorder only studies = 2, n = 319; either bipolar I or bipolar II disorder: studies = 8, n = 525), patients with either bipolar or unipolar depression in 1 study (n = 40),[39] and patients with only unipolar depression in 4 studies (n = 187).[46,50–52]

Altogether, 8 trials tested lamotrigine monotherapy, including (i) trials vs placebo[44] (studies = 5, n = 1138), (ii) trials vs lithium[46,47] (studies = 2, n = 132), and (iii) trials vs olanzapine + fluoxetine[41] (study = 1, n = 410). The remaining 10 trials (n = 472) tested lamotrigine as (i) augmentation mood stabilizers vs other active agents[48,49,53] (studies = 3, n = 70), (ii) augmentation of lithium vs placebo[54–56] (studies = 3, n = 209), and (iii) augmentation of antidepressants (studies = 4, n = 193), including paroxetine,[39,50] of a mixture of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), selective serotonin-noradrenalin reuptake inhibitors (SNRIs), and bupropion,[52] or of fluoxetine[51] vs placebo.

Target doses of lamotrigine included 400 mg/day (studies = 4) (GW603/SCAA2010[44, 47,49,50]), 250 mg/day (study = 1)[46], 200 mg/day (studies = 11), and 100 mg/day (study = 1).[51] Patients were taking lithium (studies = 8),

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TABLE 1. Study, patient, illness, and treatment characteristics on the meta-analyzed studies

Study/country	Design	Duration (weeks) - Baseline depression score	N	Completed the study	Inclusion criteria[#]	Lamotrigine	Other drug	Age (years)[a]	Female[a]	White[a]	Outcome	Analysis LOCF/ observed cases	Funding
Lamotrigine monotherapy vs placebo: 5 studies													
GW602/SCAB2001 protocol 105-602 - Calabrese1999[43] – 2008[44] - *USA, UK, France, Australia* - *Bipolar I*	R, DB, LTG vs PLC. LTG50 or 200 mg/day.	7 HAMD-17/MADRS LTG: 23.8/28.9 HAMD-17/MADRS PLC: 24.3/28.7	195 (LTG50mg = 66, 200 mg = 63, PLC = 65)	LTG50, 65%, LTG200, 71%, PLC71%	BDI, HAM-D17 > 18, MD Episode > 2weeks and < 12months	Dose: 50–200 mg. Titration: W1, 2 = 25 mg; 3 = 50; 4 = 100; 5, 7 = 200.	–	LTG 50, 41, LTG200, 42, PLC 42.4 + -12.7	LTG50, 56%, LTG200, 44%, PLC59%	LTG90%, PLC94%	HAM-D17[1], HAM-D Item1, HAM-D31, MADRS, CGI-S, I. Resp = 50% reduction MADRS	LOCF	Glaxo Smith Kline
GW603/SCAA2010 - Calabrese 2008[44] - Bipolar I, II	R, DB, LTG vs PLC.	10 HAMD-17/MADRS LTG: 24.3/28 HAMD-17/MADRS PLC: 24.5/28.2	206 (LTG103)	LTG66%, PLC67%	BDIII, HAM-D17 > 18, MD Episode > 2weeks < 12 months	Dose: 100–400 mg. Titration: w1, 2 = 25 mg; 3, 4 = 50; 5 = 100; 6 = 100-200; 7 = 100-300; 8–10 = 100–400.	–	LTG 40.5 + -11.3, PLC 40.9 + -11.2	LTG64%, PLC59%	LTG87%, PLC86%	HAM-D17[1], HAM-D Item1, HAM-D31, MADRS, CGI-S, I. Resp = 50% reduction MADRS	LOCF	Glaxo Smith Kline
SCA40910 - Calabrese 2008[44] - - Bipolar I	R, DB, LTG vs PLC.	8 HAMD-17/MADRS LTG: 23.3/29.5 HAMD-17/MADRS PLC: 23.7/29.5	257 (LTG133)	LTG61%, PLC73%	BDI, HAM-D17 > 18, MD Episode > 2weeks < 12 months	Dose: 200 mg. Titration: w1, 2 = 25 mg; 3, 4 = 50; 5 = 100; 6, 8 = 200.	–	LTG 37.6 + -12.6, PLC 37.3 + -11.5	LTG57%, PLC53%	LTG88%, PLC84%	MADRS[1], HAM-D Item1, HAM-D17, 31, MADRS, CGI-S, I. Resp = 50% reduction MADRS	LOCF	Glaxo Smith Kline
SCA100223 - Calabrese 2008[44] - Bipolar II	R, DB, LTG vs PLC.	8 HAMD-17/MADRS LTG: 24.6/29.4 HAMD-17/MADRS PLC: 24/30	221 (LTG111)	LTG73%, PLC67%	BDII, HAM-D17 > 18, MD Episode > 8weeks, > 3 either HAM-D Item 1or 7.	Dose: 200 mg. Titration: w1, 2 = 25 mg; 3, 4 = 50; 5 = 100; 6, 8 = 200.	–	LTG 38.1 + -11.5, PLC 36.5 + -11.9	LTG64%, PLC63%	LTG64%, PLC75%	MADRS[1], HAM-D Item1, HAM-D17, 31, MADRS, CGI-S, I. Resp = 50% reduction MADRS	LOCF	Glaxo Smith Kline
SCA30924 - Calabrese 2008[44] - Bipolar I	R, DB, LTG vs PLC.	8 HAMD-17/MADRS LTG: 25.4/30.6 HAMD-17/MADRS PLC: 25.3/30.8	259 (LTG131)	LTG60%, PLC57%	BDI, HAM-D17 > 18, MD Episode > 8 weeks, > 3 either HAM-D Item 1or 7, hospitalization, or incarceration for mania.	Dose: 200 mg. Titration: w1, 2 = 25 mg; 3, 4 = 50; 5 = 100; 6, 8 = 200.	–	LTG 40.5 + -12.5, PLC 38.2 + -12.1	LTG54%, PLC54%	LTG74%, PLC69%	MADRS[1], HAM-D Item1, HAM-D17, 31, MADRS, CGI-S, I. Resp = 50% reduction MADRS	LOCF	Glaxo Smith Kline
Subtotal	–	***Mean 8.2***	***Total 1138 (LTG607)***	***LTG66%, PLC67%***	***BDI 4/5, BDII 2/5.***	***Titration to at least 200 mg/day***	–	***LTG 39.47 (11.99), PLC 38.68 (11.95)***	***LTG57.8%, PLC57.6%***	***LTG80.6%, PLC81.6 %***	–	***LOCF 5/5***	**Glaxo Smith Kline *5/5***
Lamotrigine monotherapy vs lithium - 2 studies													
Schindler 2007[46] - *Germany* - *Unipolar–Resistant*	R, SB, LTG vs LIT augmentation in resistant depression.	8 HAMD-17 LTG: 22.7 HAMD-17 LIT: 21.5	34 (LTG17)	15LTG, 15PLC	Unipolar non-psychotic MDD, HAMD-17 > 17, Treatment Resistant Depression (2 AD trials failure, at adequate dose, for 6 weeks)	Dose: 150–250 mg. Titration: w1, 2 = 25 mg, w3, 4 = 50, w5 = 100, w6 = up to 250.	LIT* plasma level 0.6-0.8 mEq/L. Patients were taking or tried SSRI, SNRI, mirtazapine, AP, ECT, i-MAO, thyroid hormones supplements.	LTG 45.1 + - 13.4 LIT 50.3 + - 13.6	LTG53% PLC47%	–	HAM-D17[1], CGI. Resp = 50% reduction MADRS; remission HDRS < 7	OC	–
Suppes 2008[47] - *USA* - *Bipolar II*	R, SB, LTG vs LIT.	16 HAMD-17/MADRS LTG: 20.8/29.7 HAMD-17/MADRS LIT: 21.2/30.2	98 for anagraphic data 90 for efficacy (LTG41)	40(LTG21)	BDII acute depression HAMD17 > 18, MADRS > 18, age 18–65	Dose: up to 400 mg. Titration: w1, 2 = 25 mg; w3, 4 = 50; w5 = 75; w6 = 100; w7 = 150; w8 = 200.	LIT* plasma level 0.6–1.2 mEq/L	LTG 36.9 + - 12.3, Lit 36.2 + - 11.4	LTG68.2% LIT 57.4%	LTG75% LIT 77.8%	HAM-D17[1], MADRS, YMRS, CGI-BP, GAF. Resp = 50% reduction MADRS; remission MADRS < 8	–	–
Subtotal	–	***Mean 12***	***Total 132 (LTG58)***	***LTG69, 7%; LIT 63, 1%***	***1/2 unipolar, 1/2 BD II.***	***At least up to 250 mg/day***	***2/2 lithium, 1/2 SSRI***	***LTG39.3 (13.07) LIT 42.86 (14.23)***	***LTG57.9%, LIT 52.2%***	***LTG75% LIT 77.8%***	–	***1 OC***	–

Lamotrigine monotherapy vs other agents - 1 study													
Brown 2006[41]–2009[42] 2 studies - *USA* - *Bipolar I*	R, DB, LTG vs OLZ + FLX	7 and 25 weeks MADRS LTG: 31.4 MADRS Other: 30.9	410 (LTG205)	271 (LTG134)	BDI, MD, MADRS > 20, CGI-S > 4. Age 18-60.	Dose: 150–200.	OLZ + FLX* 6-25 to 12-50 mg/day. Allowed benztropine 6 mg, lorazepam 2 mg.	LTG 37.2 + -10.7, OLZ + FLX 36.8 + -11.5	LTG 62, 4%, OLZ + FLX 57.6%	LTG82.9%, OLZ + FLX 80.5%	CGI-S[1], MADRS, YMRS, CGI-I, GAF, BSI, MOS, PGI. Resp = 50% reduction MADRS; remission MADRS < 12	LOCF	Eli-Lilly
Lamotrigine augmentation of several antidepressants vs placebo - 4 studies													
Barbee 2011[50] - *USA* - *Unipolar-Resistant*	Phase 1: open label paroxetine vs paroxetine controlled release Phase 2: R, DB, LTGvs PLCaugmentation of paroxetine	Phase 1: 8 Phase 2: 10 HAMD-17/MADRS LTG: 22.2/27.4 HAMD-17/MADRS Other: 20.7/26.6	Phase 1: 183 Phase 2: 96 (LTG48)	65 (LTG34)	Phase 1: unipolar non psychotic depression, HAM-D17 > 18, at least 1 AD failure (defined as 6 weeks at adequate dose, 8 weeks for fluoxetine) Phase 2: HAMD17 > 15. Age 18–65. Psychotherapy was allowed, but could not have started or stopped within 12 months from trial time.	Range: 100–400 mg. Titration: W1, 2 = 25 mg; 3, 4 = 50; 5 = 100; + 100/week Mean: 271.88 + -105.45 mg/dl.	Paroxetine (range 20 mg traditional formulation to 25 mg controlled release /day, up to 50 mg or 65 mg controlled release. Zolpidem 10 mg max 2/week.	LTG 45.83 + -10.95 PLC 44.59 + -12.22	LTG68.75% PLC68.75%	–	MADRS[1], HAM-D17, CGI-S, CGI-I. Resp = 50% reduction MADRS, remission HDRS < 7	Observed; LOCF post-hoc for subgroups.	Glaxo Smith Kline
Normann 2002[39] - *Germany* - *Bipolar I, II*	R, DB, LTG vs PLCaugmentation of paroxetine	9 HAMD-21 LTG: 25.5 HAMD-21 Other: 25	40 (LTG20)	24 (LTG13)	Depressed. Age 18–65.	Dose: 200 mg. Titration: w1, 2 = 25 mg; 3, 4 = 50; 5 = 100; 6 = 150; 7 = 200.	Paroxetine 40 mg/day, lorazepam (LTG11, PLC13), and oxazepam (LTG8, PLC12).	LTG 39.6 + -15.2, PLC 37.9 + -8.49	LTG70% PLC65%	–	HAM-D21[1]· CGI-S, CGI- Resp = 50% reduction HAM-D.	LOCFI.	Glaxo Smith Kline
Santos 2008[52] - Brazil - *Unipolar-Resistant*	R, DB, LTG vs PLCaugmentation in resistant depression	8 MADRS LTG: 32.3 MADRS Other: 28.4	34 (LTG17)	27 (LTG14)	Major non-psychotic unipolar depressive episode, HAM-D17 > 17, treatment resistant depression (2 AD failure, for 6 weeks = Thase and Rush stage II)	Dose: 200 mg/. Titration: w1, 2 = 50 mg; w3, 4 = 100; w5 = 200.	LTG(TCA 4, SSRI5, VEnlaf3, Bupr1Milnacipr1); Plac (TCA3, SSRI5, Venlf4, Bupr2, Milnac2).	LTG 38.2 + -8.7 PLC 42.6 + -11.7	LTG82% PLC65%	–	MADRS[1], CGI. Resp = 50% reduction MADRS and CGI < 2	LOCF	–
Barbosa 2003[51] - South Africa - *Bipolar II-Resistant*	R, DB, LTG vs PLCaugmentation to fluoxetine in resistant depression	8 HAMD-17/MADRS LTGand HAMD-17/MADRS other: not reported	23 (LTG13)	16 (LTG9)	MD episode, at least 1 AD trial failure (at least 6 weeks at adequate dose), HAM-D17 > 18, bipolar disorder II accepted (not inclusion criteria, not exclusion criteria), age 18–65	Dose = 100 mg. Titration: w1, 2 = 25 mg; w3, 4 = 50; w5 = 100.	Fluoxetine 20 mg. Oxazepam for insomnia, anxiety.	LTG 30.2 + -8.4 PLC 34.1 + -6.9	LTG38.46% PLC60%	–	HAM-D[1], MADRS, CGI, GAF Resp = 50% reduction MADRS; remission HAMD < 7	LOCF	Glaxo Smith Kline
Subtotal	–	***Mean 8, 75***	***Total 193 (LTG98)***	***69.17% (LTG71.85%)***	***1/4 depressed, 3/4 unipolar, 1/4 BD II***	***1/4 mean LTG272 mg/dl, 2/4 200 mg/day, 1/4 100 mg/day***	***2/4 paroxetine, 1/4 fluoxetine, 1/4 SSRI, SNRI, TCA***	***LTG41.16(12.39) PLC41.51 (11.38)***	***LTG64.8%, PLC64.68%***	–	–	***3 LOCF, 1 OC***	***3 Glaxo Smith Kline***
Lamotrigine augmentation of mood stabilizers (lithium, lithium + valproate) vs placebo - 3 studies													
Van der Loos 2009[55] - *Netherlands, Spain* - *Bipolar I, II*	R, DB, LTG vs PLCaugmentation to lithium	8 MADRS LTG: 28.2 /MADRS PLC: 28.8	124(LTG64)	102 (LTG52)	BD I, II, current MD episode, MADRS > 18, CGI > 4-BP, lithium stable dose (plasma level 0.6–1.2 mEq/L) at least 2 weeks before trial, age > 18 years	Dose = 200 mg. Titration: w1, 2 = 25 mg w3, 4 = 50w5, 6 = 100w7, 8 = 200.	Lithium plasma level 0.83 + -0.16 mEq/ LLorazepam max 2 mg.	LTG 45.2 + -12.1 PLC 47.6 + -11.6	LTG58% PLC50%	–	MADRS [1], CGI-BP Resp = 50% reduction MADRS	LOCF, missing values adjusted for by the restricted maximum likelihood procedure in ANOVA	Glaxo Smith Kline
Wang 2010[56] - *USA* - *Bipolar I, II*	Phase 1: open label LIT + VPA **Phase 2**: nonresponders to phase 1 (MADRS > 20, YMRS > 12, CGI-BP-S > 4) R, DB, LTG vs PLCaugmentation. All	Phase 1: 16; Phase 2: 12 MADRS LTG: 27.6 MADRS PLC: 25.1	Phase1 98: Phase2 36 (18LTG)	16 (LTG8)	BD I or II, recent substance abuse in 3 months, rapid cycling in the last 12 months, a recent MD episode in 3 months, age 16–65 All patients in phase 2 are depressed	Phase 2 only. Dose: 200 mg Titration: w1, 2, 3, 4 = 25 mg; w5 = 50, w6 = 100; w7 = 150; w8 = 200 max	LTG; LIT min 0.5 mEq/L, mean 0.77 mEq/L, VPA min 50 mcg/ml, mean 63.7mcg/ml. PLC; LIT mean 0.74 mEq/L, VPA mean 68.06 mcg/ml. Lorazepamup to 4 mg/	LTG 34.8 + -9.1 PLC 37.6 + -11.3	LTG38.9% PLC38.9%	LTG94.4% PLC94.4%	MADRS[1]· CGI-BP, YMRS, GAF Response 50% reduction MADRS; remission MADRS < 10	LOCF	Stanley Medical Research Institute, HRSA 1

	depressed, no mixed or maniac state in phase 2, and almost all depressed also in phase 1						day, Zolpidem up to 10 mg/day.					
Kemp 2012[54] - *USA* - *Bipolar I, II*	Phase 1: open label LIT + VPA **Phase 2**: Nonresponders to phase 1 (MADRS > 19, YMRS > 12, GAF , 51) R, DB, LTG vs PLCaugmentation	Phase 1: 16 Phase 2: 12 MADRS LTG: 28.5 MADRS PLC: 27.3	Phase 1: 133 Phase 2: 49 (LTG23)	41 (19LTG)	BD I, II, rapid cycling recent MD episode, all drugs except lamotrigine-valproate suspended 4 weeks before	Phase 2 only Dose: 150–200 mg/day.	Lithium > 0.5 mEq/L, valproate > 50 mcgml Lorazepamup to 4 mg/day, Zolpidem up to 10 mg/day.	LTG 35.7 + -11 PLC 43 + -9.6	LTG52.2% PLC57.7%	LTG91.3% PLC92.3%	MADRS[1], CGI-BP, YMRS, GAF Resp = 50% reduction MADRS; remission MADRS < 10	LOCF	Stanley Medical Research Institute
Subtotal	–	***Mean 10.67***	***Total 209(LTG105)***	***70.1% (LTG69.43%)***	***3/3 BD I, 3/3 BD II***	***2/3 LTG200 mg/day, 1/3 150–200 mg/day***	***3/3 lithium, 2/3 valproate***	***LTG41.56 (12.37), PLC44.47 (11.65)***	***LTG49.8%, PLC48.87%***	***LTG92.85%, PLC93.35%***	-	***3/3 LOCF***	***1 Glaxo Smith Kline, 2 Stanley Medical Research Institute***
Lamotrigine augmentation of mood stabilizers vs other agents - 3 studies													
Nolen 2007[49] - *Netherlands -USA* - *Bipolar I, II-Resistant*	**Phase 1**: R, OL, LTG vs tranylcypromine augmentation to mood stabilizer Phase 2: Nonresponders switched to other agent	Phase 1: 10. Phase 2: 2. IDS LTG/Other: 38/32.	19 (LTG11)	11 (LTG5)	BD I or II, MD Episode, currently on mood stabilizer, at least 1 AD failure for 6 weeks	Dose: up to 400 mg. Titration: w1 = 25, w2 = 50, w3 = 100, w4 = 200, w5 = 300, w6-10 = 400. Halved if VPA, doubled if CBZ.	Lit > 0.7 mmol/l (LTG8, Tranyl 6), Valp > 50 mg/L (1, 2), CBZ > 4 mg/L (2, 0). Tranylcypromine* 20–100 mg.	LTG 46.7 + -11.6, Tranyl 45.6 + -15	LTG27.3%, Tranyl 75%	–	CGI-BP[1], IDS-C[1], YMRS. Resp = 50% reduction MADRS	LOCF	Stanley Medical Research Institute
Schaffer 2006[53] - *Canada* - *Bipolar I, II*	R, DB, LTGvs CIT augmentation to mood stabilizers	12 HAMD-17/MADRS LTGand HAMD-17/MADRS other: not reported	20 (LTG10)	12 (LTG7)	BD I, II, MD episode, age 18–65, HAMD17 > 16, mood stabilizer within 4 weeks before	Titration: w1, 2 = 25, w3, 4 = 50, w5, 6 = 100, w7, 8 = 200. halved if VPA. Dose: up to 200 mg.	CIT* Titration: w1, 2 = 10-w3, 4 = 20 Dose up to 50 mg/day. Already on Li, VPA, CBZ. Risperidone max 1 mg, gabapentin, 600, clonazepam max 2 mg, lorazepam 1 mg, zopiclone 7.5 mg, buspirone 40 mg. LIT > 0.6mmol/L, VPA > 50 mg/L, CBZ > 4 mg/L	41 + -10.5 of all 20 subjects	85% of all subjects	–	MADRS[1], HAM-D17, YMRS, CGI-I, S. Resp = 50% reduction MADRS; Remission MADRS < 8	LOCF	–
Nierenberg 2006[48] - *USA* - *Bipolar I, II-Resistant*	R, OL, LTG vs INOS vs RISP Augmentation to mood stabilizers	16 Median SUM-D LTG/inositol: 6/7.3	48 (LTG6 vs RISP 11; LTG15 vs INOS16)	–	BD I, II, not responders to at least 2 AD, or mood stabilizers + AD, age > 18, refused ECT in previous phase of STEP-BD	Titration: w1, 2 = 50; w3, 4 = 100, + 50per week.	INOS* 10-25 mg, RISP* up to 6. LIT range 06-09 mmol/L, VPA 45-90 mg/L, CBZ 4-10 mg/L, 1 or 2 AD, trazodone up to 150 mg	LTG34.5 vs RISP, 39 vs INOS. RISP33, INOS 18.5	LTG 83.3% vsRISP, 26.7% vs INOS. RISP 9.1%, INOS12.5%	LTG83.3% vsRISP, 86.7% vs INOS. RISP 9-81.8%, INOS 14-87.5%	SUM-D, SUM-M, GAF, CGI	LOCF	National Institute of Mental Health
Subtotal	–	***Mean 13.33***	***Total 70 (LTG36)***	***58.94% (LTG57.72%)***	***BD I and BD II 3/3***	***100 mg/day if VPA, 400 mg/day if CBZ***	***Lit, VPA, CBZ 3/3***	***LTG41.91 (11.23) Others 31.49 (17.34)***	***LTG46.33%, Others 57.5%***	–	–	***LOCF 3/3***	***1 Stanley Medical Research Institute, 1 NIH***
Total	–	**Mean 9.99**	**2152 (LTG1109)**	**66.07% (LTG65.57)**	**BD I 11/18, BD II 10/18, Unipolar 4/18**	**Mean LTG200 mg/day, dose halved if VPA, doubled if CBZ.**	**8/18 Lithium, 5/18 VPA, 3/18 CBZ, 1/18 INOS, 1/18 Tranylcypromine, 7/18 SSRI, 1 OLZ**	**LTG39.47 (11.92), Others-PLC 38.19 (12.52)**	**LTG56.5%, Others-PLC 56.41**	**LTG82.84%, Others-PLC 83.31%**	–	**LOCF 15/18, 2 OC**	**9 Glaxo Smith Kline, 3 Stanley Medical Research Institute, 1 Eli-Lilly, 1 NIH**

[a] = where 2 phases, data are referred to phase in **bold**.

AD = antidepressant; AP = antipsychotic; BD = bipolar disorder; BD [#] = bipolar disorder DSM-IV criteria; BSI = Brief Symptom Inventory; CBZ = carbamazepine; CGI-S/I/BP = Clinical Global Impression – Severity / Improvement / Bipolar Version; CIT = citalopram; DB = double-blind; FLX = fluoxetine; GAF = Global Assessment of Functioning scale; HAM-D17 = Hamilton Depression Rating Scale 17 Items; IDS = Inventory of Depressive Symptomatology; INOS = inositol; LIT = lithium; LOCF = last observation carried forward; LTG = lamotrigine; MADRS = Montgomery–Åsberg Depression Rating Scale; MOS = Medical Outcomes Study Short Form; OC = observed cases; OL = open label; OLZ = olanzapine; PGI = Patient Global Impression of Improvement; PLC = placebo; R = randomized; RISP = risperidone; SB = single blind; SUM-D = Sum of all Depressive items within Clinical Monitoring Form; SUM-M = Sum of all Manic items within Clinical Monitoring Form; TCA = tricyclic antidepressants; YMRS = Young Mania Rating Scale; VPA = valproic acid; * = active control drug; [1] = primary outcome.

SSRIs (studies = 7), valproate (studies = 5), carbamazepine (studies = 3), inositol (study = 1), tranylcypromine (study = 1), and olanzapine + fluoxetine (study = 1). Altogether, 10 studies were industry-sponsored (Glaxo Smith Kline: studies = 9, Eli-Lilly: study = 1), 4 were government- or foundation-sponsored (Stanley Medical Research Institute: studies = 3, National Institute for Health: study = 1), and 4 did not report any specific funding source.

Efficacy rating scales

Nine studies used MADRS and HAM-D, 5 only MADRS, 2 only HAM-D, with HAM-D being used in 11 studies (61.1%) [HAM-D 17 items: studies = 10 (55.5%), HAM-D 21 items: study = 1 (5.5%), HAM-D 31 items: studies = 5 (27.7%)]. Eleven studies (61.1%) used the Inventory of Depression Symptomatology, and 1 study used the Sum of All Depressive, Maniac Items within Clinical Monitoring Form (SUM-D) (Sachs *et al.*, 2002)[57] (5.5%). Study-defined definitions of response and remission are reported in Table 1. All efficacy outcomes are reported in Table 2.

Study quality

As reported in Supplementary Table 1 (available online), the risk of bias of the studies according to the Cochrane Collaboration tool for assessing risk of bias[34] was low in 7 of the included studies (trials reported in [39,44,55]), with high risk of bias in the remaining studies.

Trials of lamotrigine vs placebo

Primary outcome: depression score change

Lamotrigine showed significantly greater improvement in depression severity compared to placebo pooling data from 11 trials[39,44,50,52,54,55,56] (SMD = -0.15, 95% CI = -0.27, -0.02, p = 0.02; heterogeneity: p = 0.24, I^2 = 22%) (Figure 2). Results were not significantly different across subgroups of trials of lamotrigine monotherapy vs augmentation of mood stabilizers vs augmentation of antidepressants (test for subgroup differences: χ^2 = 0.04, df = 2, p = 0.98, I^2 = 0%) (Figure 2). Similarly, results were not significantly different in trials of patients with unipolar depression[50,52] vs bipolar depression[39,44,54–56] (test for subgroup differences: χ^2 = 0.28, df = 1, p = 0.60, I^2 = 0%) (Figure 3).

Since the results in placebo-controlled trials were not significantly different in the main 2 subgroup analyses and not significantly heterogeneous, we conducted further subgroup and meta-regression analyses on the primary outcome.

Subgroup analysis: study design and sponsorship effect

Double-blind vs single-blind/open studies[46–49] did not differ regarding depression score change (test for subgroup differences: χ^2 = 0.00, df = 1, P = 0.95, I^2 = 0%). Similarly, industry-sponsored[39,41,44,50,51,55] vs non-industry–sponsored studies did not differ regarding depression score change (test for subgroup differences: χ^2 = 0.00, df = 1, P = 0.95, I^2 = 0%).

Meta-regression analyses

The effect of lamotrigine vs placebo on depression ratings was not significantly moderate by age (p = 0.42), sex (p = 0.22), race (white vs other) (p = 0.683), total baseline MADRS score in lamotrigine (p = 0.74) or placebo (p = 0.93), or total baseline HAMD scores in lamotrigine (p = 0.85) or placebo groups (p = 0.62), study duration (p = 0.64), lamotrigine target dose (p = 0.10), or lamotrigine endpoint dose (p = 0.68). Also, differences in MADRS (p = 0.50) or HAMDS scores (p = 0.40) between lamotrigine and placebo groups did not seem to affect our results. However, smaller sample size was associated with significantly larger effect size (p = 0.017), with smaller studies reporting larger effect sizes (Supplemental Figure 1, available online).

Publication bias: lamotrigine vs placebo

As reported in e-Table 2, the publication bias, assessed with Egger's test[37] and Begg–Mazumdar Kendall's tau,[38] was unlikely for depressive symptom reduction and treatment response.

Secondary outcomes: treatment response

Treatment response. Lamotrigine only showed trend significance toward higher response rates compared to placebo pooling data from all 8 trials[39,50,51,52,54–56] (GW602/SCAB2001 in [44]) (RR = 1.26, 95% CI = 0.92, 1.73, p = 0.15; heterogeneity: p = 0.08, I^2 = 45%), without significant subgroup differences across lamotrigine monotherapy, lamotrigine augmentation of mood stabilizers, or lamotrigine augmentation of antidepressants (test for subgroup differences: χ^2 = 3.94, df = 2, p = 0.14, I^2 = 49.2%). Similarly, results did not differ across studies of patients with unipolar depression[50–52] vs bipolar depression[39,44,54–56] (test for subgroup differences: χ^2 = 0.08, df = 1, p = 0.77, I^2 = 0%). A funnel plot visual inspection and leave-one-out sensitivity analysis identified 1 extreme outlier.[54] After removing this study from the meta-analysis, the response rate became significantly higher in the lamotrigine group vs placebo, and heterogeneity was almost absent (RR = 1.42, 95% CI = 1.13, 1.78; p = 0.003, heterogeneity: I^2 = 2%) (Figure 4). After removal of the outlier, the number needed to treat (NNT) for response

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TABLE 2. Results of all meta-analyzed outcomes

Lamotrigine vs placebo

Outcome/subgroup	Studies	Participants	Statistical method	Effect size	Heterogeneity	Subgroup differences
Depression score change: LTG vs PLC subgroups augmented drug[39,44,50,52,54,55,56]	11	1409	Std. mean difference (IV, Random, 95% CI)	**–0.15 [–0.27, –0.02]; p = 0.02**	$\tau^2 = 0.01$; $\chi^2 = 12.74$, df = 10 (P = 0.24); $I^2 = 22\%$	Test for subgroup differences: $\chi^2 = 0.04$, df = 2 (P = 0.98), $I^2 = 0\%$
Subgroup LTG vs PLC monotherapy	5	1030		–0.13 [–0.29, 0.02], p = 0.09; $I^2 = 35\%$		
Subgroup LTG vs PLC mood stabilizer augmentation	3	209		–0.18 [–0.66, 0.30], p = 0.46; $I^2 = 65\%$		
Subgroup LTG vs PLC AD augmentation	3	170		–0.12 [–0.43, 0.18, p = 0.42; $I^2 = 0\%$]		
Depression score change: LTG vs PLC subgroup unipolar bipolar	11	1409	Std. mean difference (IV, random, 95% CI)	**–0.15 [–0.27, –0.02]; p = 0.02**	$\tau^2 = 0.01$; $\chi^2 = 12.74$, df = 10 (P = 0.24); $I^2 = 22\%$	Test for subgroup differences: $\chi^2 = 0.28$, df = 1 (P = 0.6), $I^2 = 0\%$
Subgroup LTG vs PLC unipolar	2	130		–0.06 [–0.41, 0.28]; p = 0.73; $I^2 = 0\%$.		
Subgroup LTG vs PLC bipolar	9	1279		–0.16 [–0.30, –0.02]; p = 0.03; $I^2 = 34\%$		
Response Rate: LTG vs PLC Subgroups Augmented Drug* (GW602/SCAB2001 in [44, 39,50,51,52,54,55,56])	8	529	Risk Ratio (M-H, Random, 95% CI)	**1.26 [0.92, 1.73]; p = 0.15; After sensitivity analysis 1.42 [1.13, 1.78]; p = 0.003**	$\tau^2 = 0.09$; $\chi^2 = 12.63$, df = 7 (P = 0.08); $I^2 = 45\%$	Test for subgroup differences: $\chi^2 = 3.94$, df = 2 (P = 0.14), $I^2 = 49.2\%$
Subgroup LTG vs PLC monotherapy	1	127		1.91 [1.22, 3.00]; p = 0.005;		
Subgroup LTG vs PLC mood stabilizer augmentation	3	209		0.92 [0.36, 2.37]: p = 0.87; $I^2 = 73\%$		
LTG vs PLC AD augmentation	4	193		1.13 [0.80, 1.60]; p = 0.47; $I^2 = 0\%$		
Response rate: LTG vs PLC subgroup unipolar bipolar	8	529	Risk ratio (M-H, random, 95% CI)	**1.26 [0.92, 1.73]; p = 0.15; After sensitivity analysis 1.42 [1.13, 1.78]; p = 0.003**	$\tau^2 = 0.09$; $\chi^2 = 12.63$, df = 7 (P = 0.08); $I^2 = 45\%$	Test for subgroup differences: $\chi^2 = 1.2$, df = 1 (P = 0.27), $I^2 = 16.4\%$
Subgroup LTG vs PLC unipolar	3	153		1.16 [0.74, 1.81]; p = 0.53; $I^2 = 9\%$		
Subgroup LTG vs PLC bipolar	5	376		1.27 [0.81, 1.98]; p = 0.3; $I^2 = 58\%$		
Remission rate: LTG vs PLC subgroups augmented drug[51,54,56]	3	108	Risk ratio (M-H, random, 95% CI)	0.82 [0.30, 2.24]; p = 0.70	$\tau^2 = 0.42$; $\chi^2 = 4.41$, df = 2 (P = 0.11); $I^2 = 55\%$	Test for subgroup differences: $\chi^2 = 2.89$, df = 1 (P = 0.09), $I^2 = 65.4\%$
LTG vs PLC monotherapy	0	0		Not estimable		
LTG vs PLC mood stabilizer augmentation	2	85		0.56 [0.23, 1.36]; p = 0.2; $I^2 = 27\%$		
LTG vs PLC AD augmentation	1	23		2.31 [0.59, 9.10]; p = 0.23		

Outcome/subgroup	Studies	Participants	Statistical method	Effect size	Heterogeneity	Subgroup differences
Rash: LTG vs PLC subgroups augmented drug[39,44,50,52,55,56]	10	1376	Risk ratio (M-H, random, 95% CI)	1.41 [0.99, 2.01]; p = 0.06	$\tau^2 = 0.00$; $\chi^2 = 4.15$, df = 9 (P = 0.90); $I^2 = 0\%$	Test for subgroup differences: $\chi^2 = 1.53$, df = 2 (P = 0.47), $I^2 = 0\%$
LTG vs PLC monotherapy	5	1046		1.25 [0.83, 1.88]; p = 0.29; $I^2 = 0\%$		
LTG vs PLC mood stabilizer augmentation	2	160		1.72 [0.63, 4.67]; p = 0.29; $I^2 = 0\%$		
LTG vs PLC AD augmentation	3	170		2.38 [0.87, 6.49]; p = 0.09; $I^2 = 0\%$		
Switch to mania: LTG vs PLC subgroups drug augmented[44,51,55]	4	479	Risk ratio (M-H, random, 95% CI)	1.43 [0.75, 2.74]; p = 0.27	$\tau^2 = 0.00$; $Chi^2 = 0.74$, df = 3 (P = 0.86); $I^2 = 0\%$	Test for subgroup differences: $\chi^2 = 0.74$, df = 2 (P = 0.69), $I^2 = 0\%$
LTG vs PLC monotherapy	2	332		1.68 [0.76, 3.72]; p = 0.20; $I^2 = 0\%$		
LTG vs PLC mood stabilizer augmentation	1	124		0.94 [0.29, 3.08]; p = 0.92		
LTG vs PLC AD augmentation	1	23		2.36 [0.11, 52.41]; p = 0.59		
Any AE: LTG vs PLC subgroups drug augmented[50,52,56]	3	166	Risk ratio (M-H, random, 95% CI)	1.04 [0.92, 1.18]; p = 0.54	$\tau^2 = 0.00$; $\chi^2 = 1.60$, df = 2 (P = 0.45); $I^2 = 0\%$	Test for subgroup differences: $\chi^2 = 0.08$, df = 1 (P = 0.77), $I^2 = 0\%$
LTG vs PLC monotherapy	0	0		Not estimable		
LTG vs PLC mood stabilizer augmentation	1	36		1.00 [0.67, 1.50]; p = 1		
LTG vs PLC AD augmentation	2	130		1.07 [0.88, 1.29]; p = 0.5; $I^2 = 36\%$		

Lamotrigine vs other medications with antidepressant effect

Outcome/subgroup	Studies	Participants	Statistical method	Effect size	Heterogeneity	Subgroup differences
Depression sore change: LTG vs others subgroups drug augmented[41,46–49,53]	6	612	Std. mean difference (IV, random, 95% CI)	0.02 [–0.24, 0.28]; p = 0.88;	$\tau^2 = 0.04$; $\chi^2 = 7.76$, df = 5 (P = 0.17); $I^2 = 36\%$	Test for subgroup differences: $\chi^2 = 3.49$, df = 4 (P = 0.48), $I^2 = 0\%$
LTG vs lithium	2	120		–0.26 [–1.06, 0.53]; p = 0.52; $I^2 = 72\%$		
LTG vs olanzapine + fluoxetine	1	410		0.20 [0.01, 0.40]; p = 0.04		
LTG vs tranylcypromine	1	19		0.36 [–0.56, 1.28]; p = 0.44		
LTG vs citalopram	1	19		0.09 [–0.81, 0.99]; p = 0.84		
LTG vs Inositol	1	44		–0.27 [–0.87, 0.32]; p = 0.37		
Depression score change: LTG vs others subgroups monotherapy or augmentation	6	612	Std. mean difference (IV, random, 95% CI)	0.02 [–0.24, 0.28]; p = 0.88	$\tau^2 = 0.04$; $\chi^2 = 7.76$, df = 5 (P = 0.17); $I^2 = 36\%$	Test for subgroup differences: $\chi^2 = .126$, df = 2 (P = 0.53), $I^2 = 0\%$
Monotherapy	3	530		–0.01 [–0.41, 0.39]; p = 0.95; $I^2 = 65\%$		
Augmentation to mood stabilizer	2	38		0.23 [–0.42, 0.87]; p = 0.49; $I^2 = 0\%$		
Augmentation to antidepressants	1	44		–0.27 [–0.87, 0.32]; p = 0.37		

Depression score change: LTG vs others subgroups unipolar bipolar	6	612	Std. mean difference (IV, random, 95% CI)	0.02 [-0.24, 0.28]; p = 0.88	$\tau^2 = 0.04$; $\chi^2 = 7.76$, df = 5 (P = 0.17); $I^2 = 36\%$	Test for subgroup differences: $\chi^2 = 5.21$, df = 1 (P = 0.02), $I^2 = 80.8\%$ Subgroup unipolar; only one study
Unipolar	1	30		-0.74 [-1.48, 0.01]; p = 0.05;		
Bipolar	5	582		0.15 [-0.01, 0.31]; p = 0.07; $I^2 = 0\%$		
Any AE: LTG vs PLC subgroups drug augme	6	624	Risk ratio (M-H, random, 95% CI)	0.97 [0.74, 1.29]; p = 0.85	$\tau^2 = 0.04$; $\chi^2 = 9.04$, df = 5 (P = 0.11); $I^2 = 45\%$	Test for subgroup differences: $\chi^2 = 9.02$, df = 4 (P = 0.06), $I^2 = 55.6\%$
LTG_vs_Lithium	2	124		1.25 [0.93, 1.68]; p = 0.15; $I^2 = 0\%$		
LTG_vs_ Olanzapine + Fluoxetine	1	410		0.87 [0.75, 1.00]; p = 0.05		
LTG_vs_ Tranylcypromine	1	23		0.44 [0.18, 1.09]; p = 0.08		
LTG_vs_Citalopram	1	19		0.74 [0.30, 1.80]; p = 0.51		
LTG_vs_Inositol	1	48		2.14 [0.58, 7.96]; p = 0.26		
Response: LTG vs others subgroups monotherapy or augmentation	6	624	Risk ratio (M-H, random, 95% CI)	0.97 [0.74, 1.29]; p = 0.85	$\tau^2 = 0.04$; $\chi^2 = 9.04$, df = 5 (P = 0.11); $I^2 = 45\%$	Test for subgroup differences: $\chi^2 = 4.17$, df = 2 (P = 0.12), $I^2 = 52\%$
Monotherapy	3	534		1.03 [0.77, 1.38];p = 0.84; $I^2 = 57\%$		
Augmentation to mood stabilizer	2	42		0.57 [0.30, 1.08]; p = 0.09; $I^2 = 0\%$		
Augmentation to Antidepressants	1	48		2.14 [0.58, 7.96]; p = 0.26		
Response: LTG vs others subgroups unipolar	6	624	Risk ratio (M-H, random, 95% CI)	0.97 [0.74, 1.29]; p = 0.85	$\tau^2 = 0.04$; $\chi^2 = 9.04$, df = 5 (P = 0.11); $I^2 = 45\%$	Test for subgroup differences: $\chi^2 = 0.62$, df = 1 (P = 0.43), $I^2 = = 0\%$
Unipolar	1	34		1.29 [0.62, 2.65]; p = 0.5		
Bipolar	5	590		0.97 [0.74, 1.29]; p = 0.69; $I^2 = 51\%$		

Outcome/subgroup	Studies	Participants	Statistical method	Effect size	Heterogeneity	Subgroup differences
Remission: LTG vs others subgroups drug[41,46,47,53]	4	553	Risk ratio (M-H, random, 95% CI)	0.98 [0.69, 1.41]; p = 0.92	$\tau^2 = 0.06$; $\chi^2 = 6.40$, df = 3 (P = 0.09); $I^2 = 53\%$	**Test for subgroup differences: $\chi^2 = 5.93$, df = 2 (P = 0.05), $I^2 = 66.3\%$**
LTG vs Lithium	2	124		1.28 [0.96, 1.70]; p = 0.09; $I^2 = 0\%$		
LTG vs olanzapine + fluoxetine	1	410		0.83 [0.63, 1.09]; p = 0.18		
LTG vs citalopram	1	19		0.56 [0.19, 1.59]; p = 0.27		
Remission: LTG vs others subgroups monotherapy or augmentation	4	553	Risk ratio (M-H, random, 95% CI)	0.98 [0.69, 1.41]; p = 0.92	$\tau^2 = 0.06$; $\chi^2 = 6.40$, df = 3 (P = 0.09); $I^2 = 53\%$	**Test for subgroup differences: $\chi^2 = 1.22$, df = 1 (P = 0.27), $I^2 = 18.2\%$**
Monotherapy	3	534		1.04 [0.71, 1.53]; p = 0.81; $I^2 = 62\%$		
Augmentation to mood stabilizer	1	19		0.56 [0.19, 1.59]; p = 0.27		
Any AE: LTG vs others subgroup drug[41,46,48,49,53]	5	534	Risk ratio (M-H, random, 95% CI)	0.91 [0.59, 1.40]; p = 0.67	$\tau^2 = 0.07$; $\chi^2 = 5.56$, df = 4 (P = 0.23); $I^2 = 28\%$	Test for subgroup differences: $\chi^2 = 5.08$, df = 4 (P = 0.28), $I^2 = 21.2\%$
LTG vs lithium	1	34		0.70 [0.35, 1.40]; p = 0.31		
LTG vs olanzapine + fluoxetine	1	409		2.34 [0.92, 5.98]; p = 0.07		
LTG vs Tranylcypromine	1	23		0.87 [0.54, 1.39]; p = 0.55		
LTG vs Cit	1	20		0.67 [0.14, 3.17]; p = 0.61		
LTG vs Inositol	1	48		0.64 [0.22, 1.85]; p = 0.41		
Any AE: LTG vs others subgroups monotherapy or augmentation	5	534	Risk ratio (M-H, random, 95% CI)	0.91 [0.59, 1.40]; p = 0.67	$\tau^2 = 0.07$; $\chi^2 = 5.56$, df = 4 (P = 0.23); $I^2 = 28\%$	Test for subgroup differences: $\chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$
Monotherapy	2	443		1.23 [0.35, 4.32]; p = 0.74; $I^2 = 78\%$		
Augmentation to Mood Stabilizer	3	91		0.81 [0.53, 1.23]; p = 0.33; $I^2 = 0\%$		
Switch to mania: LTG vs others subgroups drug[41,47–49,53]	5	574	Risk ratio (M-H, random, 95% CI)	1.23 [0.72, 2.11]; p = 0.45	$\tau^2 = 0.00$; $\chi^2 = 1.23$, df = 4 (P = 0.87); $I^2 = 0\%$	Test for subgroup differences: $\chi^2 = 1.22$, df = 4 (P = 0.87), $I^2 = 0\%$
LTG vs lithium	1	90		0.96 [0.42, 2.20]; p = 0.92		
LTG vs olanzapine + fluoxetine	1	393		1.32 [0.53, 3.28]; p = 0.55		
LTG vs tranylcypromine	1	23		3.93 [0.21, 73.71]; p = 0.36		
LTG vs cit	1	20		1.00 [0.07, 13.87]; p = 1		
LTG vs INOS	1	48		1.71 [0.43, 6.84]; p = 0.45		
Switch to mania: LTG vs others subgroups monotherapy or augmentation	5	574	Risk ratio (M-H, random, 95% CI)	1.23 [0.72, 2.11]; p = 0.45	$\tau^2 = 0.00$; $\chi^2 = 1.23$, df = 4 (P = 0.87); $I^2 = 0\%$	Test for subgroup differences: $\chi^2 = 0.49$, df = 1 (P = 0.48), $I^2 = 0\%$
Monotherapy	2	483		1.11 [0.60, 2.05]; p = 0.74; $I^2 = 0\%$		
Augmentation to mood stabilizer	3	91		1.76 [0.57, 5.43]; p = 0.33; $I^2 = 0\%$		

* Becomes significant after leave-one-out sensitivity analysis (Kemp *et al*[54] excluded).

AD = antidepressant, LTG = lamotrigine, N/A = not applicable, PLC = placebo.

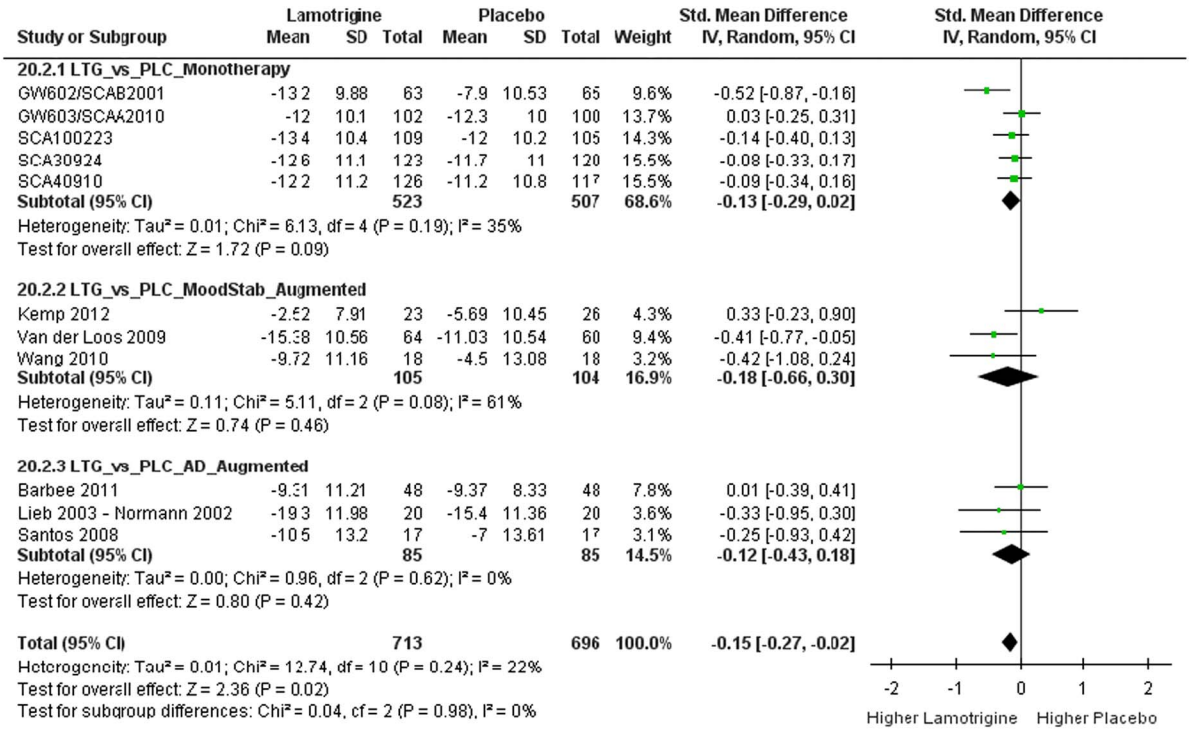

FIGURE 2. Lamotrigine vs Placebo Subgroup Drug: Depression Score Change.
LTG = Lamotrigine; PLC = placebo; MoodStab = mood stabilizers; AD = antidepressive.

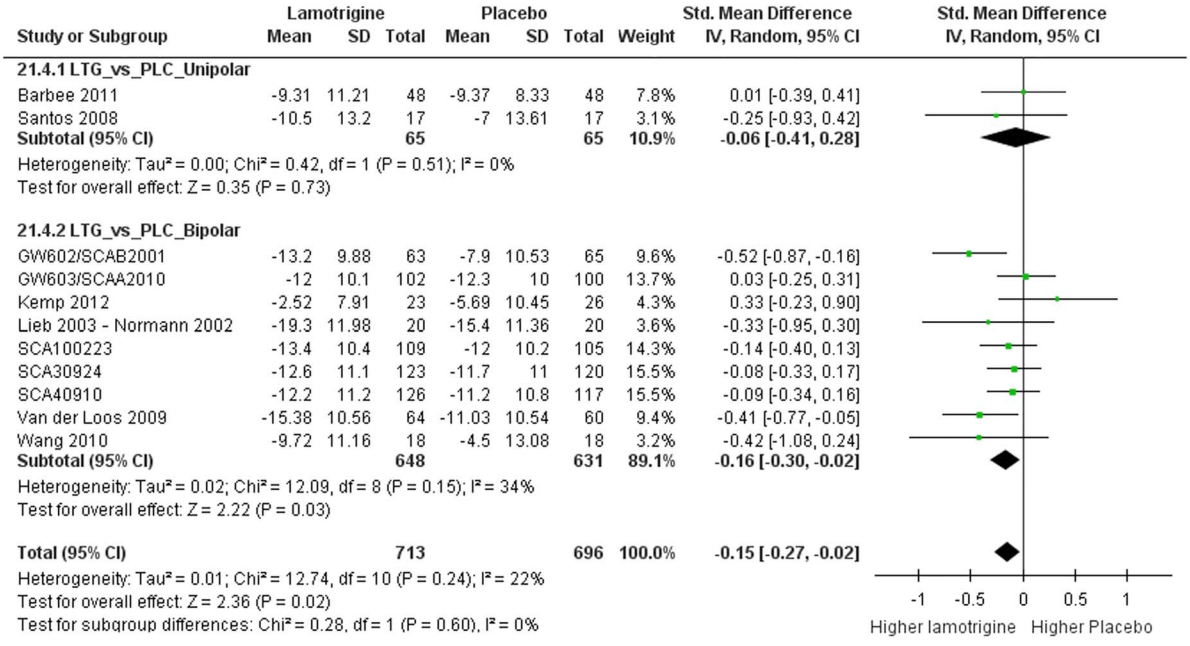

FIGURE 3. Lamotrigine vs Placebo Subgroups Uni-Bipoler: Depression Score Change

in favor of lamotrigine went from 10 (95% CI = 5.3–43) to 7 (95% CI = 4.3–17.3).

Secondary outcomes: remission. Only 3 studies provided information about remission. Remission rates were not significantly different in lamotrigine vs placebo treated patients (RR = 0.82, 95% CI = 0.30, 2.24, p = 0.70, heterogeneity: p = 0.11, I^2 = 55%).

Secondary outcomes: all-cause and specific-cause discontinuation. Overall, 66.07% of participants completed the study (lamotrigine = 65.57%, placebo = 72.8%).

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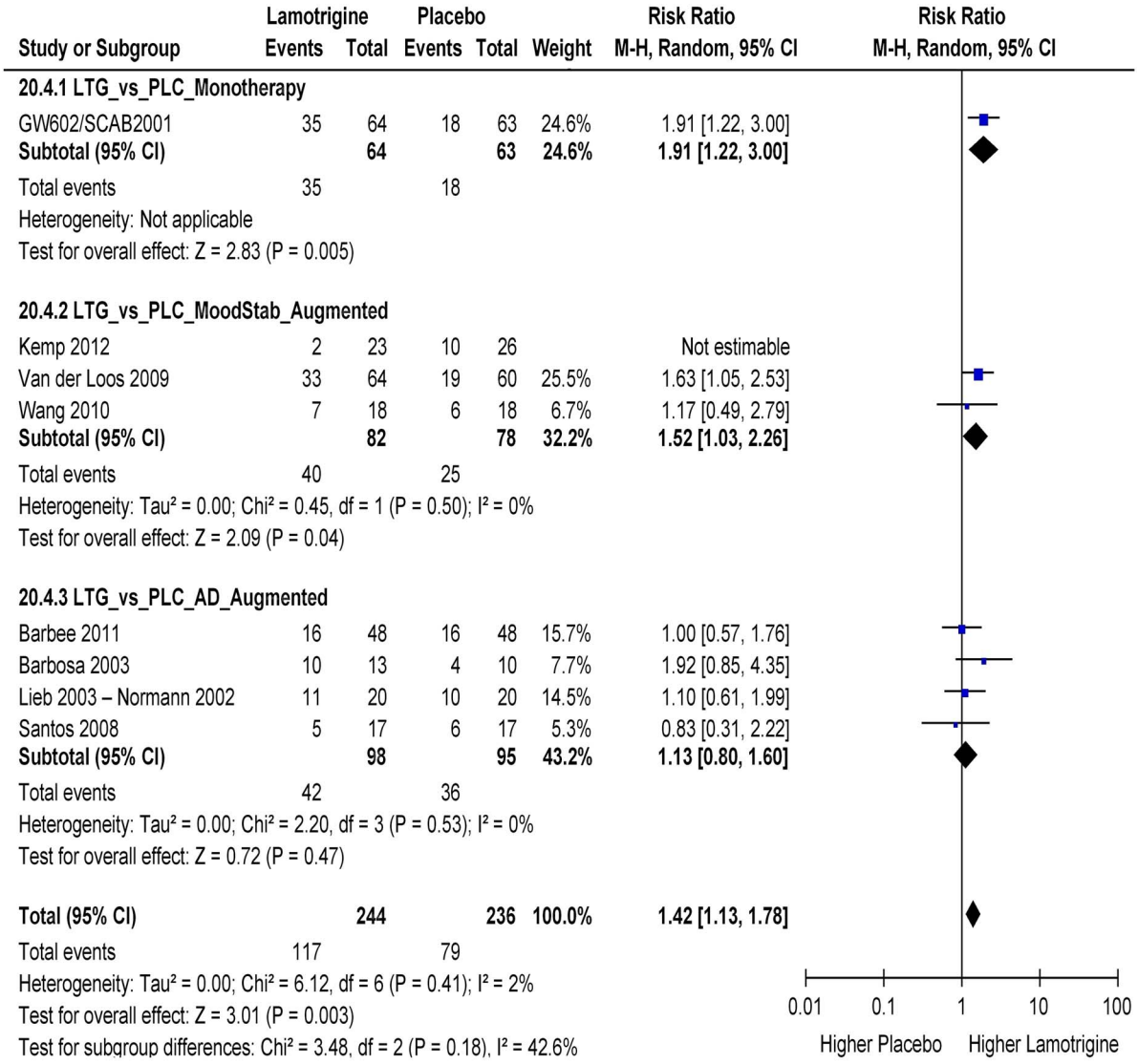

FIGURE 4. Depression Response Rates in Studies Comparing Lamotrigine vs. Placebo: Subgroup analysis by Monotherapy vs. Mood Stabilizer Augmentation vs. Antidepressants Augmentation (After Removal of One Extreme Outlier analysis.

Lamotrigine did not differ significantly from placebo regarding all-cause discontinuation (RR = 0.99, 95% CI = 0.93, 1.05, p = 0.73; heterogeneity, p = 0.8, I^2 = 0%, studies = 12), discontinuation due to inefficacy (RR = 0.71, 95% CI = 0.27-1.88, p = 0.49; heterogeneity, p = 0.26, I^2 = 25%, studies = 3), or discontinuation due to adverse events (RR = 0.93, 95% CI = 0.45, 1.92, p = 0.84; heterogeneity, p = 0.69, I^2 = 0%, studies = 12).

Secondary outcomes: safety and tolerability

The number of patients with any adverse event, number of patients switching to mania, and number of patients affected by rash were not significantly different in the lamotrigine and placebo groups (Table 2). Moreover, neither monotherapy nor augmentation therapy, nor unipolar vs bipolar depression significantly moderated the results.

Lamotrigine vs other psychotropic agents with antidepressant activity

Primary outcome: depression score change

Depression score change did not differ between lamotrigine and pooled active control groups or individual agents, ie, lithium, vs olanzapine + fluoxetine, vs citalopram, or vs inositol (Table 2). Pooled results for depression symptom change were not significantly different in monotherapy vs augmentation trials (test for subgroup differences: χ^2 = 3.49, df = 4, p = 0.48, I^2 = 0%) (Table 2). The availability of only 1 study of patients with unipolar

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depression rendered the comparison with bipolar depression not meaningless. Since the results in active-controlled trials were not significantly different and not significantly heterogeneous, we considered the pooled results valid and would have conducted subgroup and meta-regression analyses on the primary outcome; yet too few studies provided data. Based on funnel plot inspection, publication bias was unlikely.

Secondary outcomes: response and remission rates

Similar to the primary outcome, response and remission rates were also not different between the lamotrigine and active control groups (Table 2). Again, neither the comparison of lamotrigine vs lithium, vs olanzapine + fluoxetine, vs citalopram, nor vs inositol showed any significant group difference (Table 2).

Secondary outcomes: all-cause and specific-cause discontinuation

Overall, 66.1% of participants completed the study (lamotrigine = 62.6%, active controls = 63.7%). Lamotrigine did not differ significantly from other agents with antidepressant activity regarding all-cause discontinuation (RR = 0.97, 95% CI = 0.81, 1.18, p = 0.78; heterogeneity, p = 0.17, I^2 = 35%, studies = 6), discontinuation due to inefficacy (RR = 2.12, 95% CI = 0.95–4.71, p = 0.07; heterogeneity, p = 0.74, I^2 = 0%, studies = 4), or discontinuation due to adverse events (RR = 1.45, 95% CI = 0.62, 3.40, p = 0.39; heterogeneity, p = 0.79, I^2 = 0%, studies = 6).

Secondary outcomes: safety and tolerability

The number of patients with any adverse event, number of patients switching to mania, and number of patients affected by rash were not significantly different in the lamotrigine and active comparator groups (Table 2). Moreover, neither monotherapy, augmentation therapy, nor the comparison to any specific active comparator significantly moderated the results.

Discussion

Results of this meta-analysis of 18 studies and 2152 patients with unipolar or bipolar depression, treated for a mean duration of 9.83 weeks with lamotrigine or placebo or active agents with antidepressant activity, yielded the following results:

1. In placebo-controlled trials, depression rating scale scores improved significantly more with lamotrigine vs placebo, but the effect size was small.
2. After removing 1 outlying study, lamotrigine was associated with significantly higher response rates than placebo, translating into a clinically meaningful NNT of 7.
3. Depression rating improvement was not moderated by type of depression (unipolar vs bipolar) or lamotrigine monotherapy vs augmentation therapy, and these results were homogeneous.
4. None of the reported adverse effects nor all-cause or specific-cause for discontinuation differed significantly between lamotrigine and placebo.
5. In active-controlled trials, lamotrigine did not differ significantly regarding efficacy and safety from lithium, olanzapine + fluoxetine, citalopram, and inositol, separately and when pooling the active comparator groups together.

The finding of superior antidepressant efficacy compared to placebo, unmoderated by unipolar vs bipolar depression subtype and monotherapy vs augmentation strategy, suggests lamotrigine's utility in clinical care. The NNT for response of 7 is similar to that of quetiapine-IR monotherapy and lurasidone adjunctive therapy.[58] In addition, the analyzed studies included patients with more severe course of illness, such as rapid cycling and substance use disorder. Lamotrigine's safety vs placebo is an additional argument for its potential clinical utility. Nevertheless, the small overall effect size poses a problem. Because of the small effect size, we conducted several exploratory subgroup and meta-regression analyses in order to identify patient, illness, and treatment characteristic that may help clinicians to individualize lamotrigine treatment through use in subgroups or in manners that could yield larger effect sizes. However, none of the subgroup or meta-regression analyses yielded significant results, except that smaller studies yielded significantly larger effect sizes than larger studies. However, the potential publication bias suggested by the meta-regression was ruled out by specific analyses regarding publication bias.

In contrast to response, remission rates were not different between lamotrigine and placebo. However, only a few studies contributed data, and the need for the slow titration of lamotrigine may have played a role in this nonsignificant difference. Moreover, although bipolar vs unipolar depression did not appear to influence lamotrigine's acute antidepressant efficacy, the type of depression could possibly play a role in achieving the long-term goal of achieving and maintaining remission, a treatment phase where lamotrigine is often used.[59,60] Thus, further data are needed regarding the antidepressant maintenance treatment effect with lamotrigine.

Results from the active-controlled studies indicated no significant differences between lamotrigine and lithium and, especially, olanzapine + fluoxetine, which have both been shown to be effective for unipolar depression[61] and bipolar depression,[58] lending further support for the efficacy of lamotrigine in unipolar and bipolar depression.

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Several factors should be considered when interpreting these results. First of all, the meta-analyzed studies had a mean duration of around 10 weeks, but as recently pointed out,[62] such a short treatment duration is complicated by lamotrigine's slow up-titration, which may have led to a reduced signal as opposed to results in longer-term studies, and which does not allow the assessment of lamotrigine's potential maintenance and relapse preventive effects. This latter point is relevant, as for acute mania, lamotrigine has not been found to be more effective than placebo,[63,64] while it has clear relapse prevention efficacy for both bipolar mania and bipolar depression in long-term maintenance treatment studies.[15,60,65]

Nevertheless, even during the relatively short mean treatment duration of around 10 weeks, lamotrigine was effective and safe, albeit with a small effect size for the acute treatment of depression, but without the well-known risks of switch from depressive phase to manic phase possibly occurring with antidepressants,[9,13,66,67] and of weight gain and metabolic abnormalities that often are relevant with olanzapine and quetiapine[68,69] beginning even in the first few weeks of treatment.[70] Unfortunately no data about weight gain were available in the meta-analyzed studies. However, it is noteworthy that we did not find any difference in rash (Table 2) with lamotrigine vs placebo, since Stevens–Johnson syndrome is the most feared potential side effect of lamotrigine,[71,72] which generally occurs early in the treatment and titration phase with lamotrigine. Moreover, our subgroup analyses did not yield significant differences in the efficacy of lamotrigine, whether it was given as monotherapy or augmentation treatment and also independent of the specific drug that lamotrigine was added to. These results suggest that lamotrigine can be used in various combinations, obviously following the guidelines of using lower doses and titrating lamotrigine much slower when it is added to valproate due to the subsequently higher lamotrigine blood levels and increased risk for Stevens–Johnson syndrome.[73,74] Finally, including both unipolar and bipolar depression in our analysis and showing that the type of depression did not influence the efficacy of lamotrigine vs placebo indicate that lamotrigine is a safe and useful pharmacologic treatment, even in those cases where clinicians are uncertain about the type of depression.

The results of this meta-analysis clearly need to be interpreted in light of several limitations. First, the number of studies targeting unipolar depression or comparing lamotrigine with other active agents was small, the treatment duration was modest, and lamotrigine doses as well as target doses may not have always been optimal, given the need for slow titration of lamotrigine. Hence, the generalizability of the results should be considered within these constraints. Second, study design and patient population characteristics, rating scales, and outcome definitions differed considerably, which introduced variability. However, despite this clinical heterogeneity, none of the results reached statistical significance for the chi-squared test of heterogeneity. Moreover, including diverse study designs and treatment strategies allowed us to assess if these variables moderated the overall antidepressant efficacy of lamotrigine, and the results, at least of the currently available database searches, seem to suggest that lamotrigine's efficacy and safety apply to a relatively broad representation of patients that clinicians are likely to encounter in clinical care. Third, detailed data about characteristics of depressive symptoms and about the frequency of specific comorbidities were missing, although some studies allowed comorbid anxiety disorders, which precluded examination of these factors as potential moderators. Finally, the risk of bias assessment showed that only 7 studies had a low risk of bias, with high risk of bias in the remaining studies mainly due to lack of information about allocation concealment.

In summary, lamotrigine seems to be a valid management option to treat depression, possibly regardless of the baseline treatment and the type of depression. However, since at least the acute effect size was small, the mean trial duration was short, and, given the additional limitations detailed above, clearly more information is needed regarding potential subgroup and treatment characteristics as well as longer-term effects that could help individualize the management of depression with lamotrigine and yield higher effect sizes.

Disclosures

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SUPPLEMENTARY MATERIAL

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S1092852916000523

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